EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

4 December 2014
EMA/PRAC/778401/2014
Pharmacovigilance Risk Assessment Committee (PRAC)

Pharmacovigilance Risk Assessment Committee (PRAC)

Minutes of the meeting on 3-6 November 2014

Chair: June Raine – Vice-Chair: Almath Spooner

Disclaimers

Some of the information contained in these minutes is considered commercially confidential or sensitive and therefore not disclosed. With regard to intended therapeutic indications or procedure scopes listed against products, it must be noted that these may not reflect the full wording proposed by applicants and may also change during the course of the review.

Note on access to documents

Some documents mentioned in the agenda cannot be released at present following a request for access to documents under Regulation (EC) No 1049/2001 as they relate to on-going procedures for which a final decision has not yet been adopted. They will become public when adopted or considered public according to the principles stated in the Agency policy on access to documents (EMA/127362/2006).

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Explanatory notes

The Notes give a brief explanation of relevant agenda items and should be read in conjunction with the agenda.

EU Referral procedures for safety reasons: Urgent EU procedures and Other EU referral procedures
(Items 2 and 3 of the PRAC agenda)

A referral is a procedure used to resolve issues such as concerns over the safety or benefit-risk balance of a medicine or a class of medicines. In a referral, the EMA is requested to conduct a scientific assessment of a particular medicine or class of medicines on behalf of the European Union (EU). For further detailed information on safety related referrals please see:
http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000150.jsp&mid=WC0b01ac05800240d0

Signals assessment and prioritisation
(Item 4 of the PRAC agenda)

A safety signal is information on a new or incompletely documented adverse event that is potentially caused by a medicine and that warrants further investigation. Signals are generated from several sources such as spontaneous reports, clinical studies and the scientific literature. The evaluation of safety signals is a routine part of pharmacovigilance and is essential to ensuring that regulatory authorities have a comprehensive knowledge of a medicine's benefits and risks.
The presence of a safety signal does not mean that a medicine has caused the reported adverse event. The adverse event could be a symptom of another illness or caused by another medicine taken by the patient. The evaluation of safety signals is required to establish whether or not there is a causal relationship between the medicine and the reported adverse event.
The evaluation of safety signals may not necessarily conclude that the medicine caused the adverse event in question. In cases where a causal relationship is confirmed or considered likely, regulatory action may be necessary and this usually takes the form of an update of the summary of product characteristics and the package leaflet.

Risk Management Plans (RMPs)
(Item 5 of the PRAC agenda)

The RMP describes what is known and not known about the side effects of a medicine and states how these risks will be prevented or minimised in patients. It also includes plans for studies and other activities to gain more knowledge about the safety of the medicine and risk factors for developing side effects.
RMPs are continually modified and updated throughout the lifetime of the medicine as new information becomes available.

Assessment of Periodic Safety Update Reports (PSURs)
(Item 6 of the PRAC agenda)

A PSUR is a report providing an evaluation of the benefit-risk balance of a medicine, which is submitted by marketing authorisation holders at defined time points following a medicine's authorisation.
PSURs summarises data on the benefits and risks of a medicine and includes the results of all studies carried out with this medicine (in the authorised and unauthorised indications).

Post-authorisation Safety Studies (PASS)
(Item 7 of the PRAC agenda)

A PASS is a study of an authorised medicinal product carried out to obtain further information on its safety, or to measure the effectiveness of risk management measures. The results of a PASS help regulatory agencies to evaluate the safety and benefit-risk profile of a medicine.

Product related pharmacovigilance inspections
(Item 9 of the PRAC agenda)

Inspections carried out by regulatory agencies to ensure that marketing authorisation holders comply with their pharmacovigilance obligations.

More detailed information on the above terms can be found on the EMA website: www.ema.europa.eu/

Table of contents

1. Introduction

1.1. Welcome and declarations of interest of members, alternates and experts

The Chairperson opened the 3-6 November 2014 meeting by welcoming all participants.

Based on the declarations of interest submitted by the Committee members, alternates and experts and based on the topics in the agenda of the current meeting, the Committee Secretariat announced the restricted involvement of some Committee members in upcoming discussions; in accordance with the Agency's policy on the handling of conflicts of interests, participants in this meeting were asked to declare any changes, omissions or errors to their declared interests concerning the matters for discussion (see Annex II). No new or additional conflicts were declared.

Discussions, deliberations and voting took place in full respect of the restricted involvement of Committee members and experts in line with the relevant provisions of the Rules of Procedure. All decisions taken at this meeting were made in the presence of a quorum of members (i.e. 24 or more members were present in the room). All decisions, recommendations and advice were agreed unanimously, unless otherwise specified.

The PRAC Chair welcomed Magdalena Budny as the new alternate for Poland and noted the nomination of Magda Pedro as the new alternate for Portugal.

1.2. Adoption of agenda of the meeting of 3-6 November 2014

The agenda was adopted with some modifications upon request from the members of the Committee and the EMA secretariat.

1.3. Minutes of the previous PRAC meeting on 6-9 October 2014

The minutes were adopted with some amendments received during the consultation phase and will be published on the EMA website.

Post-meeting note: the PRAC minutes of the meeting held on 6-9 October 2014 were published on the EMA website on 26 November 2014 (EMA/PRAC/730503/2014).

2. EU Referral Procedures for Safety Reasons: Urgent EU Procedures

None

3. EU Referral Procedures for Safety Reasons: Other EU Referral Procedures

3.1. Newly triggered Procedures

None

3.2. Ongoing Procedures

3.2.1. **Codeine** (NAP)

- Review of the benefit-risk balance of codeine indicated for the treatment of cough in paediatric patients following notification by Germany of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)
PRAC Co-Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number: EMEA/H/A-31/1394
MAH(s): various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for codeine-containing medicines (see PRAC minutes 7-10 April 2014), relating to their indication for the treatment of cough in paediatric patients.
A preliminary assessment report was produced by the Rapporteurs in accordance with the agreed timetable.

Summary of recommendation(s)/conclusions

The PRAC discussed the preliminary assessment performed and focused on the remaining aspects to be elucidated in the review. A list of outstanding issues for the MAHs together with a revised timetable for the procedure were agreed. The PRAC considered that it would be important to seek input from the PDCO to inform the ongoing review and agreed a list of questions for them. The questions aim to gather further insight into current clinical use of codeine for the treatment of cough in children and also the impact of any potential risk minimisation. The PRAC also agreed that it was important to gather views from patients and consumers organisations (eligible to participate in EMA activities) on these aspects and supported their involvement in providing responses to some agreed questions.

3.2.2. **Hydroxyzine** (NAP)

- Review of the benefit-risk balance of hydroxyzine following the notification by Hungary of a referral under Article 31 of Directive 2001/83/EC, based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)
PRAC Co-Rapporteur: Julia Pallos (HU)

Administrative details:
Procedure number: EMEA/H/A-31/1400
MAH(s): UCB, various

Background

A referral procedure under Article 31 of Directive 2001/83/EC is ongoing for hydroxyzine-containing medicines (see PRAC minutes 10-13 June 2014). The PDCO provided a response to the PRAC list of questions.

Summary of recommendation(s)/conclusions

The PRAC discussed the responses received from the PDCO as well as the results of further data assessed by the Rapporteurs and agreed on the remaining aspects to be clarified during the review. Therefore the PRAC agreed a list of outstanding issues to be addressed by the MAHs together with a revised timetable for the procedure.

3.3. Procedures for finalisation

3.3.1. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

- Review of the benefit-risk balance of ivabradine following the notification by the European Commission of a referral under Article 20(8) of Regulation (EC) No 726/2004, based on pharmacovigilance data

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)
PRAC Co-Rapporteur: Kirsti Villikka (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000598/A20/0031, EMEA/H/C/000597/A20/0032
MAH(s): Les Laboratoires Servier

Background

A referral procedure under Article 20 of Regulation (EC) No 726/2004 for ivabradine-containing medicines Corlentor and Procoralan (see PRAC minutes of the PRAC 7-10 July 2014 for background) is to be concluded. A final assessment of the data submitted was produced by the Rapporteurs according to the agreed timetable.

Discussion

The PRAC discussed the conclusion reached by the Rapporteurs on the review performed which included the final data from the SIGNIFY study and took into consideration the advice received from the SAG, which provided input to the review.

Data from the SIGNIFY study showed that ivabradine did not have a beneficial effect on cardiovascular outcomes in patients with coronary artery disease without clinical heart failure, and therefore its use is only beneficial for symptomatic treatment.

Patients in the SIGNIFY study were started on a higher dose than recommended in the product information and received up to 10 mg twice a day, which was higher than the currently authorised maximum daily dose (7.5 mg twice a day). The data also indicated a significantly higher risk of bradycardia with ivabradine compared with placebo (17.9% vs. 2.1%). A pooled analysis of all Phase II/III double blind controlled clinical trials with a duration of at least 3 months showed that the risk of atrial fibrillation is increased in patients treated with ivabradine compared with controls (4.86% vs. 4.08%).

Regarding the small but significant increase in the primary composite endpoint (PCE) of cardiovascular death or non-fatal myocardial infarction, as seen in a subgroup of symptomatic angina patients in the SIGNIFY study, the PRAC considered it important that the individual components of the endpoint were not significantly increased. However, the PRAC concluded that ivabradine use was associated with a significantly higher risk of bradycardia than previously recognised.
Although the higher dose of ivabradine used in the SIGNIFY study did not fully explain the findings, the PRAC considered that this can have had a contributory effect, and the increase in risks of cardiovascular events in patients with angina, as observed, can be minimised by reinforcing the

recommendation not to exceed the authorised posology.
Moreover, patients with a resting heart rate < 70 bpm should be excluded from initiation of treatment because data from BEAUTIFUL study indicate that these angina patients are likely to be at higher risk of cardiovascular events.
Patients on treatment should be monitored for the occurrence of atrial fibrillation. If atrial fibrillation occurs, the balance of benefits and risks of continued ivabradine treatment should be carefully reconsidered.
Since ivabradine is only beneficial for symptomatic treatment, treatment discontinuation should be recommended in the absence of improvement in angina symptoms within 3 months.
Concomitant use of verapamil and diltiazem in patients taking ivabradine should be contraindicated in view of the dual pharmacokinetic and pharmacodynamic interaction between ivabradine and diltiazem or verapamil and the increased risk of myocardial infarction with concomitant use.

The PRAC concluded that, subject to amendments to the product information and some risk minimisation measures and additional pharmacovigilance activity, the benefit-risk balance of Procoralan/Corlentor remained favourable.

A drug utilisation study to be conducted in several EEA countries aimed at describing the characteristics of ivabradine users, as well as describing the patterns of use of ivabradine, and adherence to the risk minimisation measures, should be conducted.

Summary of recommendation(s)/conclusions

The PRAC adopted, by consensus the variation of the marketing authorisations for Procoralan and Corlentor (ivabradine) and adopted a recommendation to be considered by CHMP – see 'PRAC recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine)' EMA/676096/2014. A Direct Healthcare Professional Communication (DHPC) and communication plan were also endorsed.

Post-meeting note: the press release 'European Medicines Agency recommends measures to reduce risk of heart problems with Corlentor/Procoralan (ivabradine)' representing the opinion provided by the CHMP EMA/705247/2014 was published on the EMA website on 21 November 2014.

3.4. Article 5(3) of Regulation (EC) No 726/2004 as amended: PRAC advice on CHMP request

None

3.5. Others

None

4. Signals assessment and prioritisation[1]

4.1. New signals detected from EU spontaneous reporting systems

4.1.1. **Infliximab – INFLECTRA** (CAP), **REMICADE** (CAP), **REMSIMA** (CAP)

- Signal of rhabdomyolysis

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
EPITT 18129 – New signal
MAH(s): Hospira UK Limited (Inflectra), Janssen Biologics B.V. (Remicade), Celltrion Healthcare Hungary Kft. (Remsima)
Lead MS: SE

Background

Infliximab is a chimeric human-murine monoclonal antibody indicated for the treatment of rheumatoid arthritis, Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriatic arthritis and psoriasis.

The exposure for centrally authorised medicines containing infliximab is estimated to have been more than 4 million patient-years worldwide, in the period from first authorisation in 1999 to 2013.

During routine signal detection activities, a signal of rhabdomyolysis was identified by the EMA, based on 41 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information available on the cases of suspected rhabdomyolysis reported and considered that for some of them a causal association could not be excluded. Infliximab was used for different indications and time to onset was variable, but one case included information on a positive rechallenge. However, the PRAC agreed that more information was needed to fully assess the signal.

The PRAC appointed Ulla Wändel Liminga (SE) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for Remicade (infliximab) should submit to the EMA, within 60 days, a cumulative review of the signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.2. **Methylprednisolone** (NAP)

- Signal of hepatotoxicity after high dose intravenous use

[1] Each signal refers to a substance or therapeutic class. The route of marketing authorisation is indicated in brackets (CAP for Centrally Authorised Products; NAP for Nationally Authorised Products including products authorised via Mutual Recognition Procedures and Decentralised Procedure). Product names are listed for reference Centrally Authorised Products (CAP) only. PRAC recommendations will specify the products concerned in case of any regulatory action required

Regulatory details:
PRAC Rapporteur: Harald Herkner (AT)

Administrative details:
EPITT 18121 – New signal
MAH(s): various
Lead MS: AT

Background

Methylprednisolone is a synthetic corticosteroid with an anti-inflammatory activity used in the treatment of various conditions where corticosteroid treatment is required.

Based on current data available the exact population exposure for methylprednisolone containing intravenous solutions is difficult to calculate, however, it is estimated that at least 90 million patients worldwide have been treated in the two years period between 2009 and 2011.

During routine signal detection activities, a signal of methylprednisolone and risk of hepatotoxicity after high dose administration following intravenous use (IV) was triggered by the MAH of one of the products containing methylprednisolone. The signal was mainly based on literature screening leading to identification of 13 cases. AT, lead MS for signal management activities relating to methylprednisolone confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases of hepatotoxicity reported and agreed that assessment of causality, due to lack of specific information on these cases, was challenging.
It was also difficult to relate the reactions to a specific route of administration or a specific dosage.
Moreover several cases could be detected with prednisolone reported as co-suspected medication.
Therefore, PRAC agreed that further information was needed to fully assess the signal.

The PRAC appointed Harald Herkner (AT) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for the originator methylprednisolone containing-medicine should submit to the PRAC Rapporteur, within 60 days, a cumulative review of the signal, including for the active substance methylprednisolone, all formulations, pharmaceutical forms and routes of administration.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.1.3. Vemurafenib – ZELBORAF (CAP)

- Signal of Dupuytren's contracture

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
EPITT 18111 – New signal
MAH(s): Roche Registration Ltd
Lead MS: SE

Background

Vemurafenib is an antineoplastic agent used in the treatment of adult patients with BRAF-V600-mutation-positive unresectable or metastatic melanoma.

The exposure for Zelboraf, a centrally authorised medicine containing vemurafenib is estimated to have been more than 19 000 patients worldwide, in the period from first authorisation in 2012 to 2014.

During routine signal detection activities, a signal of Dupuytren's contracture was identified by the EMA, based on 5 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of Dupuytren's contracture reported in patients treated with vemurafenib for melanoma. None of the patients recovered and one patient also developed Peyronie's disease but in only few cases Dupuytren's contracture was considering disabling.

A case described in the literature by Sibaud et al in 2014, referred to a patient who experienced an abrupt development of bilateral Dupuytren's contracture severely impairing certain activities of daily living, 6 weeks after starting treatment with vemurafenib. The authors stated that a possible biological mechanism to explain the development of the reaction could be a paradoxical proliferation in wild type-BRAF myofibroblasts (similar to a mechanism previously described in keratinocytes and melanocytes devoid of a BRAF mutation, leading to the development of skin tumours).

The PRAC considered that, overall, generally the background incidence of the condition and its clinical relevance in this patient population made the causality assessment challenging. However, since none of the patients reported risk factors or alternative explanations for the development of the reaction, it was considered that this signal warranted further investigation.

Summary of recommendation(s)

- The MAH for Zelboraf (vemurafenib) should submit to the EMA a cumulative review of the signal which will be assessed within the PSUR ongoing procedure (PSUR DLP 16/08/2014) (submission of supplementary information by 11/02/2015).

4.1.4. Vildagliptin – GALVUS (CAP), **JALRA** (CAP), **XILIARX** (CAP)
Vildagliptin, metformin – EUCREAS (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Signal of renal failure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
EPITT 18106 – New signal
MAH(s): Novartis Europharm Ltd
Lead MS: SE

Background

Vildagliptin is dipeptidylpeptidase-4 (DPP-4) inhibitor, indicated in the treatment of type 2 diabetes mellitus in adults.

The exposure for centrally authorised medicines containing vildagliptin is estimated to have been more than 7.8 million patient-years worldwide, in the period from first authorisation in 2007 to 2014.

During routine signal detection activities, a signal of renal failure was identified by the EMA, based on 266 cases described as 'renal impairment', 'renal failure acute' and 'renal failure' retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the suspected cases of renal failure reported in association with vildagliptin and noted that in most cases patients had a medical history of renal impairment or chronic renal failure and renal function aggravated shortly after vildagliptin introduction. There were several cases describing a positive de-challenge, following newly added vildagliptin or with the fixed combination of vildagliptin/metformin.

Time-to-onset was variable, between one week to 3 months, and a temporal relationship was considered plausible; in most of the cases renal impairment (or worsening of renal impairment) was confirmed by laboratory values. In four cases HbA1c (glycated haemoglobin) was improved during the time for worsened renal laboratory values suggesting that exacerbation of diabetic nephropathy was probably not the reason for the worsening of renal impairment.

The PRAC commented that the kidney is one of the major organs contributing to vildagliptin metabolism. The main metabolic pathway of vildagliptin is hydrolysis, accounting for about 60% of the dose.
The latest PSUR reported vildagliptin as overall safe and well tolerated in patients with moderate or severe renal impairment. However, the studies in support to this were relatively small, with a total of approximately 250 patients on vildagliptin recruited. The PRAC noted that results from an additional PASS (CLAF237A1402) study conducted in Japan on safety in patients with renal impairment are awaited.
Based on this information the PRAC agreed that the signal should be further investigated and the results of the PASS analysed.

Summary of recommendation(s)

- The MAH for Galvus (vildagliptin) and Eucreas (vildagliptin/metformin) should submit to the EMA, a cumulative review of the signal and include the results from the above mentioned PASS study, as appropriate, within the next PSUR (DLP 28/2/2015).

4.2. New signals detected from other sources

4.2.1. **Aripiprazole – ABILIFY** (CAP)

- Signal of aggression and related events

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
EPITT 18127 – New signal
MAH(s): Otsuka Pharmaceutical Europe Ltd
Lead MS: PT

Background

Aripiprazole, is an antipsychotic used for the treatment of schizophrenia in adults and in adolescents aged 15 years and older, for the treatment of moderate to severe manic episodes in Bipolar I Disorder and for the prevention of a new manic episode in adults who experienced predominantly manic episodes and whose manic episodes responded to aripiprazole treatment. Aripiprazole is also used for up to 12 weeks to treat moderate to severe manic episodes in patients aged 13 years or over.

The exposure for Abilify, a centrally authorised medicine containing aripiprazole, is estimated to have been more than 8.7 million patient-years worldwide, in the period from first authorisation in 2004 to 2014.
A signal of aggression was identified by IT, following an individual case reported in Italy and an analysis of published literature and EudraVigilance data. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC considered that among the number of cases reported, some cases described a positive de-challenge and re-challenge. A possible biological mechanism had been postulated in the literature[2] and would involve the mechanism of action of aripiprazole as a partial dopamine agonist. Moreover the ADR 'aggression' is currently being closely monitored by the MAH. The PRAC concluded that it was necessary to obtain further information to assess this signal.

Summary of recommendation(s)

- The MAH for Abilify (aripiprazole) should submit to the EMA, within 60 days, a cumulative review of the signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.2. Dimethyl fumarate – TECFIDERA (CAP)

- Signal of progressive multifocal leukoencephalopathy (PML)

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
EPITT 18136 – New signal
MAH(s): Biogen Idec Ltd
Lead MS: DE

Background

Dimethyl fumarate is the dimethyl ester of fumaric acid. Tecfidera is a centrally authorised product containing dimethyl fumarate indicated for the treatment of adult patients with relapsing remitting multiple sclerosis (MS). Other products containing dimethyl fumarate, authorised nationally, are indicated for the treatment of psoriasis.

[2] Lea JW, Stoner SC, Lafollete J. Agitation associated with aripiprazole initiation. Pharmacotherapy 2007; 27(9):1339-1342.

The worldwide cumulative exposure for Tecfidera is estimated to have been more than 6,000 person-years in the clinical trial setting and, from 2013 to March 2014, is approximately 37,000 patient-years in the post-marketing setting.

A signal of progressive multifocal leukoencephalopathy (PML) was identified by DE, based on a spontaneous report of PML with fatal outcome in a patient treated with dimethyl fumarate for MS for 4.5 years in Germany. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the fatal case of PML associated with long term treatment with dimethyl fumarate and noted that cases of progressive PML had been reported in patients treated with fumaric acid esters for psoriasis.

The patient had not previously received other medicines known to be associated with a risk of PML. The diagnosis was based on clinical symptoms and the detection of JC (John Cunningham) viral DNA in the cerebrospinal fluid.
The PRAC noted that severe prolonged lymphopenia (> 3.5 years) was described in the case history. Lymphopenia, as a common adverse reaction associated with dimethyl fumarate treatment, is listed in the product information and in the RMP for Tecfidera.

Taking into account this very well described case of first occurrence of PML after long-term treatment with Tecfidera in a patient experiencing severe long-term lymphopenia and the life-threatening nature of PML, and also the case reports in EudraVigilance of PML relating to fumaric acid esters used for treatment of psoriasis, the PRAC agreed that the product information for dimethyl fumarate and esters should be updated to reflect this new information and that HCPs should be urgently informed of this case.

Furthermore additional information should be sought on this signal to inform any additional risk minimisation measures, and the PRAC agreed on a number of points to be addressed by the MAH.

Summary of recommendation(s)

- The MAH for Tecfidera should submit a proposal for a Direct Healthcare Professional Communication (DHPC) to be adopted as early as possible by CHMP.
- Variations including an updated RMP should be submitted for both Tecfidera and the nationally authorised products Fumaderm Initial and Fumaderm. A work-sharing variation involving the centrally and nationally authorised products held by the same MAH should be considered and submitted to the EMA and NCAs, providing the additional information on the signal in accordance with the questions requested.

For the full PRAC recommendations, see EMA/PRAC/683212/2014 published on the EMA website on 25/11/2014.

4.2.3. Gadoversetamide – OPTIMARK (CAP)
Gadodiamide, gadopentetic acid, gadolinium (NAP)

- Signal of nephrogenic systemic fibrosis in acute kidney injury

Regulatory details:
PRAC Rapporteur: *Rafe Suvarna (UK)*

Administrative details:
EPITT 18141 – New signal
MAH(s): Mallinckrodt Deutschland (Optimark), various
Lead MS: UK

Background

Gadolinium-containing contrast agents (GdCAs) are intravenous agents used for contrast enhancement with magnetic resonance imaging (MRI) and with magnetic resonance angiography (MRA). An Article 31 referral (see Q&A EMEA/727399/2009 rev.) for GdCAs concluded in 2010 and assessed all of the available information on the risks of NSF associated with the use of GdCAs, particularly in patients with kidney problems and patients receiving a liver transplant, neonates and infants, the elderly and pregnant or breastfeeding women. Since the conclusion of the Article 31 referral procedure, the MAHs for GdCAs have provided annual cumulative reviews of nephrogenic systemic fibrosis (NSF) cases to the Member States and the EMA.

To date, no new cases of NSF have been identified in EU that have occurred since the introduction of the EU risk minimisations measures. However, following information submitted in the context of such cumulative reviews and from the literature for one of the 'high risk' products a signal of NSF in 'acute kidney injury' (AKI) was identified by the UK. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC noted that the European Society of Urogenital Radiology guidelines (2013) stated that Gadolinium-containing contrast agents with the highest risk of NSF are contraindicated in patients with acute renal insufficiency. The American College of Radiology Manual on Contrast Media (2013) also reports information on AKI mentioning that some cases of NSF have developed in patients with AKI alone and hence AKI alone seemed to be a risk factor for NSF development.

In accordance with the latest information received from MAHs, variations were being submitted at national level to amend the existing contraindication in the product information for patients with severe renal impairment to include 'acute kidney injury (AKI)' as a separate contraindication.

The PRAC concurred that there was an apparent biological plausibility and reasoning to justify addition of the contraindication 'acute kidney injury' to the product information of 'high risk' agents; however it was also noted that current NSF risk minimisation measures in the EU so far appeared to be effective and that the evidence supporting such a contraindication needed to be clarified.

Therefore the PRAC agreed that further information on the need and modalities to update the product information should be requested.

The PRAC appointed Rafe Suvarna (UK) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAHs for the GdCAs in the 'high risk' category for NSF [Omniscan (gadodiamide), OptiMark (gadoversetamide) and Magnevist (gadopentetic acid)] should submit to the PRAC Rapporteur, an evaluation of the need to update the Contraindications and Warnings sections of SmPC with respect to acute kidney injury.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: a revised timeline submission based on justified grounds provided by the MAHs was supported by the PRAC following conclusion of the meeting.

4.2.4. **Fluvastatin, lovastatin, pitavastatin, pravastatin, simvastatin** (NAP)

- Signal of immune-mediated necrotizing myopathy (IMNM)

Regulatory details:
PRAC Rapporteur: *Arnaud Batz (FR)*

Administrative details:
EPITT 18140 – New signal
MAH(s): various
Lead MS: FR

Background

Statins are widely used agents for treating dyslipidaemia and act by competitive inhibition of the HMG-CoA reductase.

During routine signal detection activities, a signal of Immune-Mediated Necrotizing Myopathy (IMNM) was triggered by FR, based on a published article[3] suggesting that IMNM in statin-treated-patients might be a class effect, which was considered during the assessment of the PSUR for the CAP Pravafenix (pravastatin/fenofibrate). The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information available from the literature indicating that anti-HMG CoA reductase antibodies were reported in some statin-treated patients with necrotizing myopathies. Systemic immunosuppressive therapy was required in the majority of these cases for resolution of symptoms.

According to the review, several statins such as atorvastatin, simvastatin and pravastatin were involved, suggesting that this might be a class effect and not a specific statin effect.

The PRAC acknowledged that in 2012, the Pharmacovigilance Working Party had already assessed this signal as related to rosuvastatin and concluded that there was sufficient evidence to add IMNM to the product information for rosuvastatin as adverse drug reaction due to very rare reports.

Therefore the PRAC agreed that it was important to assess whether, on currently available evidence, it was possible to hypothesise that this is a class effect.

The PRAC appointed Arnaud Batz (FR) as Rapporteur for the signal.

Summary of recommendation(s)

- The PRAC Rapporteur should assess whether the new publications may change the prior conclusions of the Pharmacovigilance Working Party. Taking into account the existing text in the product information of some statins and the previously agreed rosuvastatin wording regarding immune-mediated necrotizing myopathy in association with a statin, a common wording should be discussed for all statins.

[3] Padala S, et al. Statins as possible cause of inflammatory and necrotizing myopathies. Atherosclerosis. 2012; 222: 15-21

- A 60-day timetable was recommended for this review leading to a further PRAC recommendation.

4.2.5. Octocog alfa – **HELIXATE NEXGEN** (CAP), **KOGENATE** (CAP)

- Signal of inhibitor development in previously untreated patients

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
EPITT 18134 – New signal
MAH(s): Bayer Pharma AG
Lead MS: DE

Background

Octocog alpha is an antihaemorragic medicine used in the treatment and prophylaxis of bleeding in patients with haemophilia A (congenital factor-VIII deficiency).

The exposure for Helixate and Kogenate is estimated to have been more than 142,000 patient-years worldwide, in the period from first authorisation until 2014.

Previously, an Article 20 referral procedure based on pharmacovigilance data for octocog alpha containing medicinal products, Kogenate Bayer and Helixate NexGen, had been finalised in December 2013. The Article 20 referral involving PRAC was triggered mainly by results from the RODIN[4] study which showed an increased risk for Factor VIII inhibitor development in previously untreated patients (PUP) following treatment with different products containing octocog alfa (second-generation full-length recombinant products vs third-generation products). Based on the available evidence the PRAC concluded that the data did not confirm that Kogenate Bayer or Helixate NexGen were associated with an increased risk of developing factor VIII inhibitors in PUPs, compared with other products (see EMA/108793/20144).

A signal of inhibitor development in previously untreated patients was triggered by the EMA, following the publication of two other observational prospective cohort studies conducted in France (FranceCoag; sponsored by French public health authorities)[5] and in the UK (performed by the UK Haemophilia Centre Doctors' Organisation (UKHCDO))[6] whose results were in line with the results of the RODIN study. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the data available from the literature as well as risk estimates and discussed the postulated possible biological explanation highlighted by the authors, considering the possible impact of glycosylation on immunogenicity and different biological activity of Kogenate Bayer/ Helixate Nexgen compared with Advate. The PRAC agreed that the new study results provided important additional evidence of inhibitor development in PUPs treated with Kogenate Bayer/ Helixate Nexgen versus a comparator and the data needed to be fully evaluated.

[4] Gouw SC, et al. PedNet and RODIN Study Group. Factor VIII products and inhibitor development in severe hemophilia A. N Engl J Med. 2013;368:231-9
[5] Calvez T et al. Recombinant factor VIII products and inhibitor development in previously untreated boys with severe hemophilia A, Blood. 2014 Sep 24. pii: blood-2014-07-586347
[6] Collins PW et al. Factor VIII brand and the incidence of factor VIII inhibitors in previously untreated UK children with severe haemophilia A, 2000-2011. Blood. 2014 Oct 22. pii: blood-2014-07-580498

Summary of recommendation(s)

- Having considered the previous evaluation of this issue in 2013 and the evidence from the recently published studies, the PRAC recommended that a further review of the development of inhibitors in previously untreated patients treated with recombinant human factor VIII products including octocog alfa should be performed.

4.2.6. Paliperidone – **INVEGA** (CAP), **XEPLION** (CAP)

- Signal of acute renal failure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
EPITT 18102 – New signal
MAH(s): Janssen-Cilag International N.V.
Lead MS: SE

Background

Paliperidone is an atypical antipsychotic used in the treatment of schizophrenia and psychotic or manic symptoms of schizoaffective disorder in adults.

The exposure for Invega and Xeplion, centrally authorised medicines containing paliperdone, is estimated to have been more than 2 million person-years from post-marketing experience, in the period from first authorisation until 2014.

During routine signal detection activities, a signal of acute renal failure was triggered by the EMA, following a communication of the MAH of Invega (paliperidone) regarding a recent publication in the Annals of Internal Medicine[7]. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information received on the publication on atypical antipsychotic drugs and the risk of acute kidney injury (AKI) and other adverse outcomes in older adults describing the results of a population-based retrospective cohort study performed in Canada.

The authors of the paper considered that risperidone, quetiapine and olanzapine were associated with an increased risk for AKI and with other outcomes that are known potential causes of AKI including hypotension, acute urinary retention, pneumonia, and acute cardiac events.

The PRAC noted that the EU product information of atypical antipsychotics already includes neuroleptic malignant syndrome (NMS), which is characterised by rhabdomyolysis and renal failure.
The PRAC also noted the results of a further search performed in the EudraVigilance database for paliperidone, which did not seem to suggest increased reporting of such reactions.

However the PRAC considered that more data was needed to fully assess the signal and agreed on key information to be obtained not only for paliperidone but also for other atypical antipsychotics.

[7] Hwang YJ, Dixon SN, Reiss JP, Wald R, Parikh CR, Gandhi S, Shariff SZ, Pannu N, Nash DM, Rehman F, Garg AX. Atypical antipsychotic drugs and the risk for acute kidney injury (AKI) and other adverse outcomes in older adults. Annals of Internal Medicine, 2014 Aug 19;161(4):242-8

The PRAC appointed as overall Rapporteur for the signal Qun-Ying Yue (SE).

Summary of recommendation(s)

- The MAH for Invega/Xeplion (innovator of paliperidone) and risperidone, the MAH for Zyprexa/Zyprexa Velotab/Zypadhera (innovator of olanzapine), the MAH for Abilify and Abilify Maintena (innovator of aripiprazole), the MAH for Latuda (innovator of lurasidone), the MAH for Sycrest (innovator of asenapine), the MAH for Clozaril (innovator of clozapine), the MAH for Seroquel (innovator of quetiapine), the MAH for Serdolect (innovator of sertindole), the MAH for Geodon (innovator of ziprasidone), the MAH for Zoleptil (innovator of zotepine) should submit a cumulative review of cases of 'Acute renal failure' SMQ Narrow by 10 January 2015 to the PRAC Rapporteurs.
- The Rapporteurs (for CAPs)/lead MSs (for NAPs) for individual substances provide assessment reports to PRAC and to Qun-Ying Yue (SE), the overall lead Rapporteur, within 60 days.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

Post-meeting note: a revised timeline submission based on justified grounds provided by the MAHs was supported by the PRAC following conclusion of the meeting.

4.2.7. Pantoprazole – CONTROLOC CONTROL (CAP), **PANTECTA CONTROL** (CAP), **PANTOLOC CONTROL** (CAP), **PANTOZOL CONTROL** (CAP), **SOMAC CONTROL** (CAP)

- Signal of subacute cutaneous lupus erythematosus (SCLE)

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
EPITT 18119 – New signal
MAH(s): Takeda GmbH
Lead MS: UK

Background

Pantoprazole is a proton pump inhibitor (PPI) agent, used for acid-related upper gastrointestinal disorders. Centrally authorised medicines containing pantoprazole are indicated for short-term treatment of reflux symptoms (e.g. heartburn, acid regurgitation) in adults, and their exposure is estimated to have been more than 1 billion courses of therapy worldwide, in the period from first authorisation in 2009 to 2014.

During routine signal detection activities, a signal of Subacute Cutaneous Lupus Erythematosus (SCLE) in patients treated with pantoprazole, was identified by the EMA based on 7 cases retrieved from EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the suspected cases of subacute cutaneous lupus erythematosus (SCLE) reported in association with pantoprazole. Some of the cases originated from different literature articles. Overall the cases were well documented, with supporting biopsy and serological tests. In most patients SCLE symptoms cleared between 1-2 months after stopping pantoprazole and starting symptomatic therapy.

Some cases had a plausible time to onset and showed positive rechallenge. One of these suggested a possible cross-reactivity among different proton pump inhibitors.
A plausible mechanism for the development of the reaction could imply photosensitivity which is a known adverse drug reaction related to pantoprazole.

The PRAC discussed also some further literature[8] supportive of a possible association and agreed that the signal should be further evaluated. Evidence of cross-reactivity or rechallenge at a class level should be considered during the assessment of the signal for pantoprazole, and consideration should be given to the possibility of SCLE being a class effect for proton pump inhibitors.

The PRAC appointed Rafe Suvarna (UK) as Rapporteur for the signal.

Summary of recommendation(s)

- The MAH for centrally authorised medicines containing pantoprazole, should submit by 60 days, a cumulative review of all cases of Subacute Cutaneous Lupus Erythematosus and aggravation of pre-existing SCLE in association with pantoprazole.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.2.8. Radium Ra^{223} dichloride – XOFIGO (CAP)

- Signal of cerebral haemorrhage

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
EPITT 18142 – New signal
MAH(s): Bayer Pharma AG
Lead MS: UK

Background

Xofigo is a centrally authorised therapeutic radiopharmaceutical containing radium Ra223 dichloride which is indicated for the treatment of adults with castration-resistant prostate cancer, symptomatic bone metastases and not known visceral metastases.

The exposure for Xofigo is estimated to have been more than 3000 patients worldwide, in the period from first authorisation in 2013 to 2014.

During routine signal detection activities, a signal of cerebral haemorrhage was identified by the UK, based on 15 cases reported in the United Kingdom. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information relating to the cases reported. In most cases, bleeding occurred after several doses of Radium-223 dichloride. Some cases reported decrease in platelet count or thrombocytopenia as well as a bleeding event. The potential for bone marrow suppression, and related

[8] Grönhagen CM, et al. Subacute cutaneous lupus erythematosus and its association with drugs: a population-based matched case-control study of 234 patients in Sweden. Br J Dermatol. 2012 Aug;167 (2):296-305

thrombocytopenia, neutropenia, pancytopenia, leukopenia, and lymphopenia associated with radium-223 were already reported in clinical trials and are considered known ADRs associated with the treatment. Moreover the therapeutic effect of radium-223 is mediated by a cytotoxic effect of alpha radiation on tumour cells. Therefore the PRAC agreed that there was at least one clear mechanism for haemorrhagic adverse effects as bone marrow toxicity leading to thrombocytopenia may increase the risk of bleeding events. However, as a reduced platelet count was not reported in some cases, alternative pathophysiological mechanisms should also be considered. In light of these considerations the PRAC agreed that the signal should be further evaluated, with a view to updating the product information.

Summary of recommendation(s)

- The MAH for Xofigo (radium-223 dichloride) should submit to the EMA a cumulative review of cerebral haemorrhage and related MedDRA terms within the next PSUR (DLP 14/11/2014).

4.2.9. Sorafenib – NEXAVAR (CAP)

- Signal of acute generalised exanthemantous pustulosis (AGEP)

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
EPITT 18109 – New signal
MAH(s): Bayer Pharma AG
Lead MS: SE

Background

Sorafenib is antineoplastic agent used for the treatment of hepatocellular carcinoma, renal cell carcinoma and differentiated thyroid carcinoma.

The exposure for Nexavar, a centrally authorised medicine containing sorafenib, is estimated to have been more than 300 000 patients worldwide, in the period from first authorisation in 2009 to 2013.

During routine signal detection activities, a signal of acute generalised exanthemantous pustulosis (AGEP) was identified by the EMA, triggered by some newly published case reports[9] which prompted a further search in EudraVigilance. The Rapporteur confirmed that the signal needed initial analysis and prioritisation by the PRAC.

Discussion

The PRAC discussed the information on the cases described. Acute generalised exanthematous pustulosis (AGEP) is a type IVd hypersensitivity with 1-5 cases per million per year and PRAC commented that there was a possibility that misclassification between AGEP and other dermatological toxicities may occur. The PRAC also commented that a pattern suggestive of a temporal relationship was apparent in some cases; some of them had a positive rechallenge and hypersensitivity could be

[9] Pretel M, Iñarrairaegui M, Lera JM, Aguado L, Idoate MA: Acute generalized exanthematous pustulosis induced by sorafenib. JAMA Dermatol. 2014 Jun;150(6):664-6.
Liang CP, Yang CS, Shen JL, Chen YJ. Sorafenib-induced acute localized exanthematous pustulosis in a patient with hepatocellular carcinoma. Br J Dermatol. 2011 Aug;165(2):443-5

considered a plausible biological mechanism to explain the reaction. Therefore the PRAC agreed that the signal should be further investigated.

Summary of recommendation(s)

- The MAH for Nexavar (sorafenib) should submit to the EMA, within 60 days, a cumulative review of the signal.
- A 60-day timetable was recommended for the assessment of this review leading to a further PRAC recommendation.

4.3. Signals follow-up and prioritisation

4.3.1. Bisphosphonates (CAP, NAP): **alendronate** (NAP); **risedronate** (NAP); **alendronate, colecalciferol – ADROVANCE** (CAP), **FOSAVANCE** (CAP), **VANTAVO** (CAP) **Strontium ranelate – OSSEOR** (CAP), **PROTELOS** (CAP)

- Signal of heart valve disorders

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
EPITT 13832 – Follow-up July 2014
MAH(s): Merck Sharp & Dohme Limited (Adrovance, Fosavance, Vantavo), Les Laboratoires Servier (Osseor, Protelos), various

Background

For background information, see PRAC minutes of 7-10 July 2014.
The Rapporteur assessed the clarification received on the results of the EMA commissioned study on the risk of cardiac valve disorders associated with the use of bisphosphonates.

Discussion

The PRAC discussed the clarification received on the study and commented on the potential role of confounding due to the underlying disease which could not be excluded as a possible explanation for the study findings. The appropriateness of a common study design in view of the heterogeneous nature of the data sources analysed was questioned. In addition, despite the further clarifications and information provided, residual confounding remained a concern, particularly given the small risks found. Therefore the PRAC concluded that overall the currently available evidence did not appear to support a causal relationship between bisphosphonates or strontium ranelate and increased risk of cardiac valve disorders.

Summary of recommendation(s)

- The PRAC agreed that no changes were necessary to the product information of bisphosphonate or strontium ranelate-containing products. The MAHs should continue to monitor cardiac valve disorders as part of routine pharmacovigilance activities.

4.3.2. Leuprorelin, suspension for injection (NAP)

- Signal of medication error - wrong technique in drug usage process

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
EPITT 17753 – Follow-up September 2014
MAH(s): Astellas (Eligard)

Background

For background information, see PRAC minutes of 8-11 September 2014. The MAH replied to the request for information on the signal of medication error - wrong technique in drug usage process – associated with cases of lack of clinical efficacy that were assessed by the Rapporteur and submitted related variations as requested by the PRAC, to be assessed by the RMS.

Discussion

The PRAC discussed the replies received from the MAH and one oral explanation took place at the meeting. The PRAC discussed the current plan for risk minimisation and remaining areas to be elucidated on the different measures proposed to reduce the risk of medication errors. The PRAC stressed that the risk management plan should be updated in regards to this signal and discussed the content of a DHPC to report that lack of clinical efficacy may occur due to incorrect reconstitution of the product. Finally, PRAC agreed that device modification to improve its functioning and minimise errors in the reconstitution phase was needed.

Summary of recommendation(s)

- The MAHs of Eligard (leuprorelin) should distribute a direct healthcare professional communication (DHPC) according to the text and communication plan agreed by the PRAC.
- The MAH should submit by December 2014 a variation modifying the device.
- The MAH should submit an update of the Risk Management Plan with appropriate routine and additional pharmacovigilance and risk minimisation measures regarding the risk of lack of clinical efficacy due to medication error.

For the full PRAC recommendations, see EMA/PRAC/683212/2014 published on the EMA website on 25/11/2014.

4.3.3. Sildenafil – **REVATIO** (CAP), **VIAGRA** (CAP)

- Signal of increased risk of incident melanoma

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
EPITT 17997 – Follow-up July 2014
MAH(s): Pfizer Limited

Background

For background information, see PRAC minutes of 7-10 July 2014.
The MAH replied to the request for information on the signal of increased risk of incident melanoma and the responses were assessed by the Rapporteur.

Discussion

The PRAC discussed the data received, consisting of a review of epidemiologic and medical literature, preclinical findings, published mechanistic studies, analysis of all sildenafil clinical trials as well as post-marketing safety data, patient exposure data, and a statistical disproportionality analysis of the MAH safety databases.

The review showed that non-clinical data did not support a causal mechanism, clinical studies and post-marketing data did not indicate an increased risk for melanoma skin cancer in sildenafil users, and that no plausible biological mechanism was confirmed.

In light of the findings and in consideration of a substantial limitation in the study by Li et al. (the signal trigger) the PRAC considered, as previously highlighted, that there was not enough data to indicate, or support, a causal role for sildenafil on increased risk of melanoma.

Summary of recommendation(s)

- No changes to the product information of sildenafil containing medicines are required at this point in time. The MAHs should continue to monitor any suspected cases of melanoma reported as part of routine pharmacovigilance.

4.3.4. Vildagliptin – GALVUS (CAP), **JALRA** (CAP), **XILIARX** (CAP)
Vildagliptin, metformin – EUCREAS (CAP), **ICANDRA** (CAP), **ZOMARIST** (CAP)

- Signal of interstitial lung disease

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
EPITT 17793 – Follow-up June 2014
MAH(s): Novartis Europharm Ltd

Background

For background information, see PRAC minutes of 10-13 June 2014.

Following the recommendation of the PRAC to submit a variation to address the signal of interstitial lung disease (ILD) by updating the product information, the MAH submitted further clarification regarding ILD and proposed that no changes in the product information were necessary. These responses were assessed by the Rapporteur.

Discussion

The PRAC acknowledged the clarification provided which, in addition to information on the market exposure of vildagliptin in Japan versus the rest of the world, changed the interpretation of the findings. The publication by Koo et al, suggesting that in the WHO data analysis (1992-2001) healthcare professionals in Japan used the term 'pneumonia interstitial' preferentially for adverse drug reactions that were classified as 'pneumonia' by healthcare professionals in other countries, was acknowledged. Taking into account the confounding factors in a majority of the cases and the clarified market exposure of vildagliptin in Japan versus the rest of the world, combined with the awareness of discussions regarding increased reporting rate of ILD predominately from Japanese post-marketing cases for other substances, the PRAC reconsidered its earlier conclusion and agreed that there was

insufficient evidence to suspect a causal association of vildagliptin and ILD and recommended that, at present, ILD should not be included in 4.8 of the SmPC but instead be closely monitored in future PSURs.

Summary of recommendation(s)

- There is insufficient evidence for an association between vildagliptin and interstitial lung disease (ILD) to warrant an update of the product information at the present time. However the MAH for vildagliptin-containing medicines should closely monitor ILD in future PSURs.

5. Risk Management Plans

5.1. Medicines in the pre-authorisation phase

5.1.1. Apremilast

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003746
Intended indication(s): Treatment of psoriatic arthritis, psoriasis

5.1.2. Dasabuvir

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003837
Intended indication(s): Treatment of chronic hepatitis C

5.1.3. Edoxaban

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002629
Intended indication(s): Prevention of stroke and systemic embolism and treatment of venous thromboembolism

5.1.4. Human alpha1-proteinase inhibitor

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002739
Intended indication(s): Treatment to slow the underlying destruction of lung tissue

5.1.5. Human fibrinogen, human thrombin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002807
Intended indication(s): Adjunct to haemostasis

5.1.6. Mifepristone

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002830*, Orphan*
Intended indication(s): Treatment of signs and symptoms of endogenous Cushing's syndrome in adults

5.1.7. Oritavancin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003785
Intended indication(s): Treatment of complicated skin and soft tissue infections (cSSTI)

5.1.8. Plasmodium falciparum circumsporozoite protein fused with hepatitis B surface antigen (rts), and combined with hepatitis B surface antigen (s) in the form of non-infectious virus-like particles (vlps) produced in yeast cells (saccharomyces cerevisiae) by recombinant DNA technology

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/W/002300
Intended indication(s): Active immunisation against malaria

5.1.9. Tedizolid

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002846
Intended indication(s): Treatment of tissue infections (cSSTI)

5.1.10. Tolvaptan

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002788, *Orphan*
Intended indication(s): Treatment of kidney disease (ADPKD)

5.2. Medicines already authorised

RMP in the context of a variation[10] – PRAC-led procedure

See Annex 14.1

RMP in the context of a variation – CHMP-led procedure

5.2.1. Deferiprone – FERRIPROX (CAP)

- Evaluation of an RMP in the context of a variation

[10] In line with the revised variation regulation for submissions as of 4 August 2013

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000236/II/0089/G
Procedure scope: Update of SmPC section 4.5 regarding the combination of deferiprone with other iron chelators further to a request of the PRAC in the assessment of the PSUR (PSUV/083). Update of SmPC section 5.1 and the RMP with the results of study LA37-111 conducted to evaluate the effect of deferiprone on cardiac QT and QTC interval duration
MAH(s): Apotex Europe BV

Background

Ferriprox, is a centrally authorised product containing deferiprone, indicated for the treatment of iron overload in patients with thalassaemia major when deferoxamine therapy is contraindicated or inadequate. Following assessment of the PSUR in April 2014 it was recommended that the MAH should also consider updating the product information regarding concomitant use with other iron chelators.

Therefore the CHMP is evaluating a type II variation procedure for Ferriprox, regarding the combination of deferiprone with other iron chelators and other aspects. The PRAC is responsible for providing advice to the CHMP on the necessary updates to the RMP to support this variation.

Summary of advice

- The RMP version 8.1 for Ferriprox (deferiprone) in the context of the variation under evaluation by the CHMP was considered acceptable provided that an updated version addressing some clarifications is provided before finalisation of the variation procedure by the CHMP.
- The PRAC noted letters from patient organisations on the patient perspective regarding review of iron chelation combination therapy and lack of evidence of harm, received in the context of the ongoing evaluation of the procedure.

5.2.2. Ferumoxytol – RIENSO (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002215/II/0008
Procedure scope: Extension of indication to add all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion As a consequence, SmPC sections 4.1, 4.2, 4.4, 4.8 and 5.1 were proposed to be updated
MAH(s): Takeda Pharma A/S

Background

Rienso is a centrally authorised product containing ferumoxytol a colloidal iron-carbohydrate complex indicated for the intravenous treatment of iron deficiency anaemia in adult patients with chronic kidney disease (CKD).

The CHMP is evaluating an extension of the therapeutic indication for Rienso, a centrally authorised product containing ferumoxytol, to include all cause iron deficiency anaemia when oral therapy is ineffective or inappropriate or where there is a need for rapid iron repletion. The PRAC is responsible

for providing advice to the CHMP on the necessary updates to the RMP to support this extension of indication.

Summary of advice

- The RMP version 3.4 for Rienso (ferumoxytol) submitted in the context of the extension of indication under evaluation by the CHMP was considered acceptable provided an updated version is submitted with some recommended corrections. Further issues that need to be addressed within the ongoing PSUR procedure were also agreed.

RMP evaluated in the context of a PSUR procedure

See also Colestilan – BINDREN 15.1.6. ; Histamine dihydrochloride – CEPLENE 15.1.12. ; Olanzapine – ZYPADHERA 15.1.19. ; Parecoxib – DYNASTAT 15.1.21. ; Regadenoson – RAPISCAN 6.1.12.

RMP evaluated in the context of PASS results

See also Pioglitazone – ACTOS, GLUSTIN, pioglitazone, glimepiride – TANDEMACT, pioglitazone, metformin – COMPETACT, GLUBRAVA 16.1.8. and 16.1.9. ; Regorafenib – STIVARGA 16.1.10.

RMP evaluated in the context of a renewal of the marketing authorisation, conditional renewal or annual reassessment

See ANNEX 14.

RMP evaluated in the context of a stand-alone RMP procedure

None

6. Periodic Safety Update Reports (PSURs)

6.1. Evaluation of PSUR procedures[11]

6.1.1. Alogliptin – VIPIDIA (CAP)
alogliptin, metformin – VIPDOMET (CAP)
alogliptin, pioglitazone – **INCRESYNC** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002182/PSUV/0007, EMEA/H/C/002178/PSUV/0008
MAH(s): Takeda Pharma A/S

[11] Where a regulatory action is recommended (variation, suspension or revocation of the terms of Marketing Authorisation(s)), the assessment report and PRAC recommendation are transmitted to the CHMP for adoption of an opinion. Where the PRAC recommends the maintenance of the terms of the marketing authorisation(s), the procedure finishes at the PRAC level

Background

Alogliptin is a dipeptidyl peptidase 4 (DPP-4) inhibitor, which is indicated and alone or in combinations in adults aged 18 years and older with type 2 diabetes mellitus under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Vipidia, Vipdomet and Incresync, centrally authorised medicines containing alogliptin and combinations, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Vipidia, Vipdomet and Incresync (alogliptin and combinations) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to amend the existing warning on hypersensitivity to reflect that erythema multiforme has been observed in the post-marketing setting. In addition, erythema multiforme should be added as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[12].
- In the next PSUR, the MAH should provide detailed reviews of cases of hepatotoxicity and cases of intestinal obstruction.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.2. Cidofovir – VISTIDE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Margarida Guimarães (PT)

Administrative details:
Procedure number(s): EMEA/H/C/000121/PSUV/0044
MAH(s): Gilead Sciences International Ltd

Background

Cidofovir is a cytidine analogue indicated for the treatment of cytomegalovirus (CMV) retinitis in adults with acquired immunodeficiency syndrome (AIDS) under certain conditions.

The PRAC adopted its assessment report of the PSUR and noted the marketing authorisation(s) for the concerned products had been withdrawn at the request of the MAH (Commission Implementing Decision of 22.8.2014).

6.1.3. Diphtheria (D), tetanus (T), pertussis (acellular, component) (Pa), hepatitis B (rDNA) (HBV), poliomyelitis (inactivated) (IPV) and haemophilus influenzae type b (Hib) conjugate vaccine (adsorbed) – HEXACIMA (CAP), **HEXAXIM** (Art 58), **HEXYON** (CAP)

- Evaluation of a PSUR procedure

[12] Update of SmPC sections 4.4 and 4.8. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002702/PSUV/0011, EMEA/H/W/002495/PSUV/0019, EMEA/H/C/002796/PSUV/0013
MAH(s)/Scientific Opinion Holder(s): Sanofi Pasteur

Background

Diphtheria, tetanus, pertussis (acellular, component), hepatitis B (rDNA), poliomyelitis (inactivated) and haemophilus influenzae type b conjugate vaccine (adsorbed) (DTaP-IPV-HB-Hib) is indicated for primary and booster vaccination of infants and toddlers from six weeks to 24 months of age against diphtheria, tetanus, pertussis, hepatitis B, poliomyelitis and invasive diseases caused by *Haemophilus influenzae type b* (Hib).

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Hexacima, Hexaxim and Hexyon, DTaP-IPV-HB-Hib vaccines, and issued a recommendation on their marketing authorisation(s)/scientific opinion.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Hexacima, Hexaxim and Hexyon (DTaP-IPV-HB-Hib vaccines) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s)/scientific opinion(s) should be maintained.

The PRAC discussed recent publications[13] on pertussis resurgence following the use of acellular pertussis-containing vaccines and agreed to refer the issue to the CHMP to consider involvement of the Vaccine Working Party (VWP) for further evaluation.

Acellular pertussis containing vaccines

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.4. Exenatide – **BYDUREON** (CAP), **BYETTA** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002020/PSUV/0024, EMEA/H/C/000698/PSUV/0045
MAH(s): AstraZeneca AB

[13] Mooi Fr et al.: Pertussis resurgence: waning immunity and pathogen adaptation – two sides of the same coin. Epidemiol. Infect. (2014), 142, 685–694.
Van der Maas NAT et al. Pertussis in the Netherlands, is the current vaccination strategy sufficient to reduce disease burden in young infants? Vaccine 31 (2013) 4541– 4547

Background

Exenatide is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated in combination for the treatment of type 2 diabetes mellitus and as an adjunctive therapy to basal insulin under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Bydureon and Byetta, centrally authorised medicines containing exenatide, and issued a recommendation on their marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Bydureon and Byetta (exenatide) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to revise a warning on the occurrence of cholelithiasis, linked to rapid weight loss during exenatide treatment. In addition, with regard to Bydureon, the section on undesirable effects should be revised based on the frequency of adverse reactions identified from clinical trials and spontaneous reports experienced with exenatide administered once weekly only. Therefore the current terms of the marketing authorisation(s) should be varied[14].
- In the next PSUR, the MAH should provide detailed reviews of cases of goitre and worsening/enlargement of goitre, gastrointestinal haemorrhage, rectal haemorrhage and related-haemorrhage reactions and of spontaneous reports of disorientation and update the product information accordingly as warranted. In addition, the MAH should recalculate the frequencies of adverse reactions based on its updated clinical database. With regard to Byetta specifically, the MAH should provide a detailed discussion on the number of events from post-marketing reports in line with estimation of frequency as detailed in the Guideline on Summary of Product Characteristics (SmPC). Finally, the MAH should continue to closely monitor the reporting rate for cases of pancreatitis, pancreatic cancer, thyroid cancer, serious bullous conditions/skin reactions, injection site abscesses and cellulitis.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.5. Fenofibrate, pravastatin – **PRAVAFENIX** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/001243/PSUV/0012
MAH(s): Laboratoires SMB S.A.

[14] Update of SmPC sections 4.4 and 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Fenofibrate/pravastatin in combination (Pravafenix) is indicated for the treatment of high risk coronary heart disease (CHD) adult patients with mixed dyslipidaemia under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Pravafenix, a centrally authorised medicine containing fenofibrate/pravastatin, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Pravafenix (fenofibrate/pravastatin) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- In the next PSUR, the MAH should closely monitor cases of musculoskeletal adverse events, neoplasms, cataract/myasthenia gravis, and any cases and literature reports on statins and immune-mediated necrotizing myopathy.
  See also under new signal, HMG-CoA reductase inhibitors 4.2.4. **Error! Reference source not found.**

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.6. Golimumab – SIMPONI (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000992/PSUV/0058
MAH(s): Janssen Biologics B.V.

Background

Golimumab is a tumour necrosis factor alpha (TNF-α) inhibitor indicated for the treatment of rheumatoid arthritis (RA), psoriatic arthritis (PsA), ankylosing spondylitis (AS), ulcerative colitis (UC) under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Simponi, a centrally authorised medicine containing golimumab, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Simponi (golimumab) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to refine the instructions for administration to clarify the functioning of the prefilled pen auto-injector. Therefore the current terms of the marketing authorisation(s) should be varied[15].
- In the next PSUR, the MAH should provide a detailed review of cases of glioblastoma. In addition, in the next update of the RMP, the MAH should upgrade sarcoidosis from an important potential risk to an important identified one.

The frequency of PSUR submission should be revised from yearly to three-yearly and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.7. Granisetron – SANCUSO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jolanta Gulbinovic (LT)

Administrative details:
Procedure number(s): EMEA/H/C/002296/PSUV/0034
MAH(s): ProStrakan Limited

Background

Granisetron is a serotonin 5-HT_3 receptor antagonist indicated in adults for the prevention of nausea and vomiting associated with moderately or highly emetogenic chemotherapy under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Sancuso, a centrally authorised medicine containing granisetron (as a transdermal patch), and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Sancuso (granisetron transdermal patch) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypersensitivity reactions as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[16].
- In the next PSUR, the MAH should provide detailed reviews of cases of drug ineffectiveness and medication error as well as any complaints on patch adherence-related issues. In addition, the MAH should provide an updated RMP to add serotonin syndrome as an important potential risk as previously recommended and to delete hypersensitivity reactions from the list of identified risks.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

[15] Update of SmPC section 6. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[16] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

6.1.8. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000758/PSUV/0070
MAH(s): Novartis Vaccines and Diagnostics GmbH

Background

Optaflu is an influenza vaccine (surface antigen, inactivated, prepared in cell cultures) indicated for the prophylaxis of influenza for adults, especially in those who are at an increased risk of influenza-associated complications.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Optaflu, a centrally authorised influenza vaccine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Optaflu (influenza vaccine (surface antigen, inactivated, prepared in cell cultures)) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add extensive limb swelling as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[17].
- In the next PSUR, the MAH should continue to clearly distinguish specific adverse events associated with Optaflu and provide detailed reviews, as relevant, of any unexpected findings or trends that could be indicative of differences in adverse event profile, efficacy, or effectiveness between cell-based and egg-based seasonal influenza vaccines.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.9. Ivabradine – **CORLENTOR** (CAP), **PROCORALAN** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000598/PSUV/0032, EMEA/H/C/000597/PSUV/0033
MAH(s): Les Laboratoires Servier

[17] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion

Background

Ivabradine is a heart rate lowering agent which acts purely on the sinoatrial (SA) node indicated in the treatment of coronary artery disease and of chronic heart failure in selected patients.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Corlentor and Procoralan, centrally authorised medicines containing ivabradine, and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- The PRAC recommendation following the assessment of the current PSURs is without prejudice to the outcome of the procedure under Article 20 of Regulation (EC) 726/2004 (see 3.3.1. **Error! Reference source not found.**).
- Based on the review of the data on safety and efficacy presented in the PSUR, excluding the impact of the findings from the SIGNIFY study assessed within the procedure under Article 20, the risk-benefit balance of Corlentor and Procoralan (ivabradine) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH should closely monitor cases of peripheral oedema. The MAH should also provide a detailed review of cases of visual acuity reduced and consider updating the product information as warranted. In addition, the MAH should continue to closely monitor cases of cardiac and cardio-respiratory arrest, cases of conduction disorders other than atrio-ventricular block, as well as cases of coronary artery disorders.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.10. Lurasidone – LATUDA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002713/PSUV/0002
MAH(s): Takeda Pharma A/S

Background

Lurasidone is a selective dopamine and monoamine antagonist indicated for the treatment of schizophrenia in adults aged 18 years and over.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Latuda, a centrally authorised medicine containing lurasidone, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Latuda (lurasidone) in the approved indication(s) remains favourable.

- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[18].

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.11. Macitentan – OPSUMIT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): EMEA/H/C/002697/PSUV/0003
MAH(s): Actelion Registration Ltd.

Background

Macitentan is an endothelin receptor antagonist indicated, as monotherapy or in combination, for the long-term treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO functional class (FC) II to III.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Opsumit, a centrally authorised medicine containing macitentan, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Opsumit (macitentan) in the approved indication(s) remains favourable.
- Nevertheless, the product information should be updated to add hypersensitivity as an undesirable effect with an unknown frequency. Therefore the current terms of the marketing authorisation(s) should be varied[19].
- In the next PSUR, the MAH should provide detailed reviews of oedema and fluid retention, nasal congestion and symptomatic hypotension. The MAH should also provide detailed information for the adverse drug reactions reported in off–label use. In addition, the MAH should include a detailed discussion regarding safety data collected in the DUAL[20] studies in patients with ischaemic digital ulcers associated with systemic sclerosis.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.12. Regadenoson – RAPISCAN (CAP)

- Evaluation of a PSUR procedure

[18] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[19] Update of SmPC section 4.8. The package leaflet is updated accordingly. The PRAC AR and PRAC recommendation are transmitted to the CHMP for adoption of an opinion
[20] Treatment of Digital Ulcers in Systemic Sclerosis Patients (DUAL-1 and DUAL-2): multicentre, double-blind two-period study with an initial fixed 16-week Period 1, followed by a Period 2 of variable duration

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001176/PSUV/0015 (with RMP version 6.0)
MAH(s): Rapidscan Pharma Solutions EU Ltd.

Background

Regadenoson is a selective coronary vasodilator indicated as a pharmacological stress agent for radionuclide myocardial perfusion imaging (MPI) in adult patients unable to undergo adequate exercise stress testing.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Rapiscan, a centrally authorised medicine containing regadenoson, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Rapiscan (regadenoson) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- Considering the recently identified risks of cerebrovascular accident (CVA) and prolongation of regadenoson-induced seizures following administration of aminophylline, the PRAC supported communication of the previously agreed risk minimisation measures to healthcare professionals via a Direct Healthcare Professional Communication (DHPC) from the MAH.
- In the next PSUR, the MAH should provide a detailed review of cases of respiratory arrest and consider proposing updates to the product information as warranted.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.13. Somatropin – NUTROPINAQ (CAP), **OMNITROPE** (CAP), **SOMATROPIN BIOPARTERS** (CAP), NAP

- Evaluation of a PSUSA[21] procedure

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002772/201403
MAH(s): Ipsen Pharma, Sandoz GmbH, BioPartners GmbH, various

Background

Somatropin is a recombinant DNA-derived human growth hormone (GH) indicated for the treatment of children with inadequate endogenous GH to stimulate linear growth and increase growth rate, as well as for the maintenance in adults and children of a normal body composition by increasing nitrogen retention and stimulation of skeletal muscle growth, and by mobilisation of body fat.

[21] PSUR single assessment, referring to CAP, NAP

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of somatropin-containing products and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of somatropin-containing products in the approved indication(s) remains favourable. In August 2014, the French SAGhE[22] group published an article identifying an increased risk of stroke (primarily haemorrhagic) amongst patients treated with growth hormone during childhood. Due to several limitations of the study, a causal relationship between GH treatment and stroke was considered not established at present. The PRAC considered that the need for regulatory action should be reviewed when the results of the European SAGhE study, the final French SAGhE dataset, as well as data and analyses from large studies from an individual company, become available (expected in 2015).
- The current terms of the marketing authorisations should be maintained.

In order to enable an early assessment of these additional data, the frequency of PSUR submission should be reduced from three-yearly to 18 months and the next PSUR should be submitted to the EMA within 90 days of the data lock point. The list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC is updated accordingly.

6.1.14. Telmisartan, amlodipine – TWYNSTA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/001224/PSUV/0021
MAH(s): Boehringer Ingelheim International GmbH

Background

Telmisartan/amlodipine combination is indicated for the treatment of essential hypertension in adults as add-on therapy and as replacement therapy under certain conditions.

Based on the assessment of the PSUR, the PRAC reviewed the benefit-risk balance of Twynsta, a centrally authorised medicine containing telmisartan/amlodipine, and issued a recommendation on its marketing authorisation(s).

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of Twynsta (telmisartan/amlodipine) in the approved indication(s) remains favourable.
- The current terms of the marketing authorisation(s) should be maintained.
- The MAH should submit to EMA within 60 days a detailed review of cases of interstitial lung disease (ILD).

[22] Safety and Appropriateness of Growth hormone treatments in Europe

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.15. Telmisartan – KINZALMONO (CAP), **MICARDIS** (CAP), **PRITOR** (CAP), NAP
Telmisartan, hydrochorothiazide – KINZALKOMB (CAP), **MICARDISPLUS** (CAP), **PRITORPLUS** (CAP), NAP

- Evaluation of a PSUSA[23] procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002882/201404
MAH(s): Bayer Pharma AG (Kinzalkomb, Kinzalmono, Pritor, PritorPlus), Boehringer Ingelheim International GmbH (Micardis, MicardisPlus), various

Background

Telmisartan is an angiotensin II receptor antagonist and alone or in combination with hydrochorothiazide is indicated for the treatment of essential hypertension, for the reduction of cardiovascular morbidity in adults under certain conditions and in adults whose blood pressure is not adequately controlled on telmisartan alone.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of telmisartan- and telmisartan/hydrochlorothiazide-containing products[24] and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of telmisartan- and telmisartan/hydrochlorothiazide-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- In the next PSUR, the MAH should provide detailed reviews of cases of hyponatraemia, paraesthesia, dizziness, rhabdomyolysis. In addition, MAHs should provide a detailed review of cases of off label exposure to telmisartan during pregnancy.

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.1.16. Tenofovir – VIREAD (CAP), NAP

- Evaluation of a PSUSA[25] procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

[23] PSUR single assessment, referring to CAP, NAP
[24] Including products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, as requested by Competent Authorities [DIR Article 107b (3b)] and reflected in the EURD list for the current PSUSA procedure
[25] PSUR single assessment, referring to CAP, NAP

Administrative details:
Procedure number(s): EMEA/H/C/PSUSA/00002892/201403
MAH(s): Gilead Sciences International Ltd, various

Background

Tenofovir is a nucleoside monophosphate analogue indicated in combination for the treatment of HIV-1 infected paediatric patients under certain conditions.

Based on the assessment of the individual PSURs, part of the PSUR single assessment procedure (PSUSA), the PRAC reviewed the benefit-risk balance of tenofovir-containing products[26] and issued a recommendation on their marketing authorisations.

Summary of recommendation(s) and conclusions

- Based on the review of the data on safety and efficacy, the risk-benefit balance of tenofovir-containing products in the approved indication(s) remains favourable.
- The current terms of the marketing authorisations should be maintained.
- With regard to Viread and Tenofovir Zentiva, MAHs should provide in the next PSUR a detailed discussion on the possible relationship between the revision of the frequency of renal monitoring and an increase of the frequency or the severity of renal events. MAHs should also provide a detailed review of cases of pregnancy exposure.
- With regard to Viread, the MAH should provide in the next PSUR detailed progress reports on studies NCT01488526 and NCT01745822 exploring the prevention of perinatal transmission of hepatitis B virus (HBV). In addition, the MAH should provide a detailed review on bone safety of in utero exposed neonates taking into account results from the IMPACCT P1084 study (NCT01066858)[27] and study CO-US-104-0420 (presented by *Siberry et al*[28]*).*

The next PSUR should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC.

6.2. Follow-up to PSUR procedures[29]

See Annex 15.1

7. Post-authorisation Safety Studies (PASS)

7.1. Protocols of PASS imposed in the marketing authorisation(s)[30]

7.1.1. **Domperidone** (NAP)

- Evaluation of an imposed PASS protocol

[26] Including products referred to in Articles 10(1), 10a, 14, 16a of Directive 2001/83/EC as amended, as requested by Competent Authorities [DIR Article 107b (3b)] and reflected in the EURD list for the current PSUSA procedure
[27] IMPACCT study P1084: maternal and infant monitoring for evidence of toxicity related to tenofovir exposure: the bone and kidney health substudy of the IMPAACT 1077 PROMISE protocol (promoting maternal and infant survival everywhere)
[28] Substudy of the surveillance monitoring for ART toxicities (SMARTT) study of the paediatric HIV/AIDS cohort study (PHACS), reported at the 2014 CROI conference
[29] Follow-up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure
[30] In accordance with Article 107n of Directive 2001/83/EC

Regulatory details:
PRAC Rapporteur: *Patrick Maison (FR)*

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0008
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study (drug utilisation study) in routine clinical practice to assess the effectiveness of the risk minimisation measures and to monitor off-label use of domperidone as per the conclusions of the Article 31 referral
MAH(s): Pierre Fabre Medicament (Domperidone Pierre Fabre, Oroperidys, Peridys)

Background

According to the conclusion of a referral under Article 31 of Directive 2001/83/EC for domperidone containing medicines (see PRAC AR EMA/152501/2014 and ANNEX IV) marketing authorisation holders are to conduct a drug utilisation study to assess the effectiveness of the risk minimisation measures and to monitor off-label use. A MAH (see above) submitted a draft protocol for assessment by the PRAC.

Conclusion

The PRAC appointed Patrick Maison (FR) as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for the procedure.

7.1.2. Domperidone (NAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Patrick Maison (FR)

Administrative details:
Procedure number(s): EMEA/H/N/PSP/0009
Procedure scope: Evaluation of a protocol for a non-interventional post-authorisation safety study (drug utilisation study) in routine clinical practice to assess the effectiveness of the risk minimisation measures and to monitor off-label use of domperidone as per the conclusions of the Article 31 referral
MAH(s): Rottapharm (Domperidona Gamir)

Background

According to the conclusion of a referral under Article 31 of Directive 2001/83/EC for domperidone containing medicines (see PRAC AR EMA/152501/2014 and ANNEX IV) marketing authorisation holders are to conduct a drug utilisation study to assess the effectiveness of the risk minimisation measures and to monitor off-label use. A MAH (see above) submitted a draft protocol for assessment by the PRAC.

Conclusion

The PRAC appointed Patrick Maison (FR) as PRAC Rapporteur for the assessment of the protocol and agreed a timetable for the procedure.

7.1.3. Umeclidinium bromide – INCRUSE (CAP)
umeclidinium bromide, vilanterol – ANORO (CAP), **LAVENTAIR** (CAP)

- Evaluation of an imposed PASS protocol

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/PSP/J/0003
Procedure scope: Evaluation of an imposed PASS protocol (study 201038): non-interventional observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in chronic obstructive pulmonary disease (COPD) patients with umeclidinium/vilanterol compared with tiotropium as a condition of the licence
MAH(s): Glaxo Group Ltd

Background

Incruse, is a centrally authorised medicine containing umeclidinium bromide; Anoro/Laventair are centrally authorised products containing the combination umeclidinium bromide, vilanterol indicated as a maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD). As part of the conditions or restrictions with regard to the safe and effective use of the medicinal product (ANNEX II of the MA) a post-authorisation safety (PAS) observational cohort study to quantify the incidence and comparative safety of selected cardiovascular and cerebrovascular events in COPD Patients with these products compared with tiotropium, should be conducted. A protocol for the study was submitted by the MAH and was assessed by the Rapporteur.

Endorsement/Refusal of the protocol

The PRAC, having considered the draft protocol version 1 - in accordance with Article 107n of Directive 2001/83/EC, objected to the draft protocol for the above listed medicinal product(s). The overall research objectives and methods were considered acceptable but a number of concerns regarding milestones, variables and study design and planned analysis should be resolved before the final approval of the study protocol.

The PRAC therefore recommended that:

- The MAH should submit a revised PASS protocol within 60 days to the EMA. A 60 days-assessment timetable will be applied.

7.2. Protocols of PASS non-imposed in the marketing authorisation(s)[31]

See Annex 16

7.3. Results of PASS imposed in the marketing authorisation(s)[32]

None

7.4. Results of PASS non-imposed in the marketing authorisation(s)[33]

See Annex 16

[31] In accordance with Article 107m of Directive 2001/83/EC, supervised by PRAC in accordance with Article 61a (6) of Regulation (EC) No 726/2004
[32] In accordance with Article 107p-q of Directive 2001/83/EC
[33] In accordance with Article 61a (6) of Regulation (EC) No 726/2004, in line with the revised variations regulation for any submission as of 4 August 2013

7.5. Interim results of imposed and non-imposed PASS and results of non-imposed PASS submitted before the entry into force of the revised variations regulation[34]

See Annex 16

8. Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

8.1.1. Denosumab – PROLIA (CAP)

- PRAC consultation on a five-year renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/001120/R/0043 (with RMP)
MAH(s): Amgen Europe B.V.

Background

Denosumab is human monoclonal antibody (IgG2) indicated for the treatment of osteoporosis in postmenopausal women and in men at increased risk of fractures, and for the treatment of bone loss associated with hormone ablation in men with prostate cancer at increased risk of fractures.

Prolia, a centrally authorised medicine containing denosumab, was authorised in 2010.

The MAH submitted an application for renewal of the marketing authorisation for opinion by the CHMP. The PRAC is responsible for providing advice to the CHMP on this renewal with regard to safety and risk management aspects.

Summary of advice

Based on the review of the available pharmacovigilance data for Prolia and the CHMP Rapporteur's assessment report, the PRAC considered that a second five-year renewal of the marketing authorisation(s) is warranted on the basis of pharmacovigilance grounds currently under review, including fracture healing complications, cardiovascular events, primary malignancy, osteonecrosis of the jaw, cases of osteonecrosis of the jaw (OJ), serious infections and atypical femoral fracture.

See also under 5.2

9. Product related pharmacovigilance inspections

9.1. List of planned pharmacovigilance inspections

None

[34] In line with the revised variations regulation for any submission before 4 August 2013

9.2. On-going or concluded pharmacovigilance inspection

Disclosure of information on results of pharmacovigilance inspections could undermine the protection of the purpose of these inspections, investigations and audits. Therefore such information is not reported in the agenda.

9.3. Others

10. Other Safety issues for discussion requested by the CHMP or the EMA

10.1. Safety related variations of the marketing authorisation (MA)

10.1.1. **Mycophenolate mofetil – CELLCEPT** (CAP)

- PRAC consultation on a safety-related variation, upon CHMP request

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000082/II/0119
Procedure scope: Update of SmPC sections 4.4 and 4.8 of the SmPC following assessment of SDA036 in order to add a warning and update the safety information on bronchiectasis and hypogammaglobulineamia. The package leaflet is updated accordingly. The MAH also provided with a DHPC as requested by the PRAC
MAH(s): Roche Registration Ltd

Background

Following a previously evaluated signal of bronchiectasis and hypogammaglobulinaemia for mycophenolate mofetil (see PRAC minutes 10-13 June 2014) a proposal for a DHPC was submitted by the MAH, which was assessed by the Rapporteur in the framework of a type II variation to update the product information.

Summary of advice

The PRAC provided comments on the key messages of the DHPC and agreed that the same text could be applicable for other products containing mycophenolate mofetil and mycophenolic acid. Therefore all MAHs should be encouraged to send a single DHPC with the same content.

10.2. Timing and message content in relation to MS safety announcements

None

10.3. Other requests

None

11. Other Safety issues for discussion requested by the Member States

11.1. Safety related variations of the marketing authorisation

11.1.1. **Flupirtine** (NAP)

- PRAC consultation on variation, upon Germany's request

Regulatory details:
Lead member: Martin Huber (DE)

Administrative details:
Procedure number(s): AB/H/XXX/II/XXX
Procedure scope: PRAC involvement in the evaluation of an RMP (version 1.0) following the implementation of the Commission Decision dated 5 September 2013 of the article 107i referral procedure on flupirtine
MAH(s): Teva Pharma B.V. (Katadolon retard)

Background

An obligation for submitting an RMP for flupirtine containing medicines was included in annex IV of the Commission implementing decision dated 5 September 2013 following the conclusion of an Article 107i referral procedure. In particular the MAH(s) were requested to submit the core elements (including outline of DUS, PASS and educational materials) of a risk management plan in EU format within 3 months after the EC decision.

The MAH for Katadolon retard, a purely nationally authorised medicinal product containing the active substance flupirtine, has submitted the first version of a RMP (version 1.0) to the individual MSs.

DE requested PRAC advice with the aim to harmonise assessment of the RMP version 1 across the various MSs.

Summary of advice

The PRAC supported a proposal for a harmonised assessment of the RMP and recommended a harmonised core RMP for all flupirtine containing products. The inclusion of the following safety concerns were considered appropriate: drug induced liver injury as an Important identified risk, off-label use in long-term treatment greater than 2 weeks as an 'Important potential risk' and use during pregnancy and lactation as 'Missing information'. Likewise, the inclusion of the requested DUS and PASS as well as the educational material for prescribers and patients as 'additional pharmacovigilance/risk minimisation activities', as a result of the 2013 referral, was also endorsed.

11.2. Renewals of the Marketing Authorisation

None

11.3. Other requests

11.3.1. **Clarithromycin** (NAP)

- PRAC consultation on a PSUR worksharing procedure upon Ireland's request

Regulatory details:
Lead member: Almath Spooner (IE)

Administrative details:
Procedure number(s): IE/H/PSUR/0020/003
Procedure scope: PRAC involvement in the evaluation of a PSUR worksharing procedure regarding the cardiovascular safety of clarithromycin
MAH(s): Abbott (Klacid), various

Background

During the 7-10 October 2013 meeting, the PRAC discussed the follow-up to the signal of cardiovascular (CV) adverse events with clarithromycin. The P-RMS had circulated a preliminary assessment of the MAH's response, as part of a PSUR work-sharing procedure addressing the PRAC recommendations. Ireland requested PRAC advice on this assessment.

Summary of advice

Based on the review of the available information the PRAC recommended that a study-level meta-analysis to further investigate the CV safety of clarithromycin should be performed. Ideally this would be based on individual patient data, and be conducted promptly. Proposed changes to the product information, based on the outcome of the review performed, were endorsed and should be implemented within the ongoing work-sharing procedure.

Regarding the need for research at class level, the PRAC considered that there is not an urgent concern to justify a particular research strategy now, but the issue may need review as more data become available.

12. Organisational, regulatory and methodological matters

12.1. Mandate and organisation of the PRAC

12.1.1. PRAC meeting under the Italian presidency of the council of the EU

At the organisational matters teleconference on 19 November 2014, the IT PRAC member presented a report of the PRAC meeting held in Rome organised by the Italian Agency (AIFA) under the Italian Presidency of the EU on regulatory and strategic pharmacovigilance matters. Topics included registries and drug safety, pharmacovigilance decision making, the PRAC experience after 2 years of operation and a joint session with CMDh to discuss strategic issues of mutual interest. Members congratulated Italy for organising a successful meeting and agreed some actions to be taken forward that will be considered in the framework of the PRAC work plan.

Pharmacovigilance audits and inspections

None

12.2. Periodic Safety Update Reports & Union Reference Date (EURD) List

12.2.1. Periodic Safety Update Reports

- Consultation on the handling of PSUR single assessment for Nationally Approved Products only

The PRAC noted the final version of the 'CMDh standard operating procedure on the processing of PSUR single assessment procedures for nationally authorised products'. The document will be published on the CMDh webpages of the Heads of Medicines Agencies website.

12.2.2. Union Reference Date List

- Consultation on the draft list, version November 2014

At the organisational matters teleconference on 19 November 2014, EMA secretariat presented the November 2014 version of the list together with an overview of the expected workload relating to upcoming PSUSA procedures involving purely nationally authorised medicines starting in 2015. It was explained that a workshop is to be organised by the EMA to address the PSUR single assessment for allergen products.

The PRAC endorsed the draft revised EURD list version November 2014 reflecting the PRAC comments impacting the DLP and PSUR submission frequencies of the substances/combinations. The PRAC endorsed the newly allocated Rapporteurs for upcoming PSUSAs in accordance with the principles previously endorsed by the PRAC (see PRAC Minutes April 2013).

Post-meeting note: following the PRAC meeting in November 2014, the updated EURD list was adopted by the CHMP and CMDh at their November 2014 meeting and published on the EMA website on 01/12/2014 (see:

Home> Human Regulatory>Pharmacovigilance>Periodic safety update reports>EURD list> List of Union reference dates and frequency of submission of periodic safety update reports (PSURs))

12.3. Signal Management

12.3.1. Signal Management

- Feedback from Signal Management Review Technical (SMART) Working Group

The PRAC was informed of the topics discussed by the SMART WG, which included the circumstances when a synchronised approach between innovator and generic products as regards the implementation of labelling changes would be preferable (whenever the innovator for a substance affected by a signal is not a CAP); feedback from the recently held training for pharmacovigilance assessors at the EMA on signal assessment procedure; and organisational aspects relating to better exchange of information within the network for signal assessment procedures.

12.4. Adverse Drug Reactions reporting and additional reporting

12.4.1. List of Product under Additional Monitoring

- Consultation on the draft list, version November 2014

The PRAC was informed of the updates made to the list of products under additional monitoring.

Post-meeting note: The updated additional monitoring list was published on 26/11/2014 on the EMA website (see: Home>Human Regulatory>Human medicines>Pharmacovigilance>Signal management>List of medicines under additional monitoring)

12.5. EudraVigilance Database

None

12.6. Risk Management Plans and Effectiveness of risk Minimisations

None

12.7. Post-authorisation Safety Studies

12.7.1. Post-Authorisation Safety Studies

- Non-imposed PASS protocols – proposal for a revised process

This topic was deferred to the December 2014 PRAC meeting.

12.8. Community Procedures

None

12.9. Renewals, conditional renewals, annual reassessments

None

12.10. Risk communication and Transparency

None

12.11. Continuous pharmacovigilance

None

12.12. Interaction with EMA Committees and Working Parties

12.12.1. Blood Products Working Party (BPWP)

- Guideline on core SmPC for human plasma derived recombinant coagulation factor IX products

A draft revision of the guideline (Rev.2) following public consultation was circulated to PRAC for comments. The PRAC was kindly invited to present comments in writing

12.12.2. Blood Products Working Party (BPWP)

- Guideline on core SmPC for plasma-derived fibrin sealant/haemostatic products

The EMA secretariat presented a draft revision of the guideline which describes the information to be included in the Summary of Product Characteristics (SmPC) for plasma-derived fibrin sealant / haemostatic products which takes into account the conclusion reached during the referral procedures (Article 20 of Regulation (EC) No 726/2004 and Article 31 of Directive 2001/83/EC) for fibrin sealants (see Q&A EMA/734308/2012 rev.1). The comments provided by the PRAC will be consolidated and submitted to the BPWP.

12.12.3. Healthcare Professionals' Working Party (HCPWP)

- Work plan 2015

At the organisational matters teleconference on 19 November 2014, the PRAC endorsed the HCPWP work plan for 2015 and welcomed the opportunities of further dialogues and interaction with representatives of healthcare professionals, academia and learned societies, as described in the revised work plan.

12.12.4. Patients' and Consumers' Working Party (PCWP)

- Work plan 2015

At the organisational matters teleconference on 19 November 2014, the PRAC endorsed the PCWP work plan for 2015 and fully endorsed the value of the strengthened involvement of patient and consumer organisation in a wide array of EMA activities.

Interaction within the EU regulatory network

12.12.5. EU Regulatory Network Strategy for Best Evidence

- Reflection paper on a strategy for best evidence

At the organisational matters teleconference on 19 November 2014, the EMA secretariat outlined a strategy paper to support the use of best evidence and knowledge management to support regulatory decision making and to supplement activities and data provided by MAHs. The PRAC discussed existing resources and agreed that more can be done to further utilise existing data sources of information and the knowledge available in pharmacovigilance. The development of a reflection paper on best evidence was supported and some members volunteered to support this. In particular the development of a working group of individuals from the EMA and NCAs with experience in methodologies and statistics and directly accessing Electronic Health Records (EHR) databases was supported by the PRAC.

12.12.6. Post-Authorisation Safety Studies

- EU collaborative framework for patient registries

At the organisational matters teleconference on 19 November 2014, following circulation to the PRAC members for initial comments, EMA secretariat presented an updated proposal for a strategy and pilot phase for an EU Collaborative Framework for Patient Registries. Next steps to be considered were described, such as a cross-committee group to finalise strategy paper, how to develop methodological guidance as well as relevant parties to be involved. Further discussion will take place at the next meeting of the PRAC.

12.13. Contacts of the PRAC with external parties and interaction of the EMA with interested parties

None

12.14. Others

None

13. Any other business

13.1. New organisational model: Review of the Initial marketing authorisation applications (MAA) process

At the organisational matters teleconference on 19 November 2014, EMA secretariat provided a progress report on the re-design of the process for assessment of new marketing authorisation applications. PRAC welcomed enhanced involvement in the redesign of the RMP assessment process and requested additional details on expected timelines for revision of relevant templates and guidance documents. A more detailed update will be scheduled for the December 2014 PRAC meeting.

14. ANNEX I Risk Management Plans

Medicines in the pre-authorisation phase

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of the RMP for the below mentioned medicines under evaluation for initial marketing authorisation application. Information on the medicines containing the below listed active substance will be made available following the CHMP opinion on their marketing authorisation.

14.1.1. Aripiprazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003926, *Generic*
Intended indication(s): Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.2. Aripiprazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003803, *Generic*
Intended indication(s): Treatment of schizophrenia in adults and in adolescents aged 15 years and older

14.1.3. Aripiprazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/004008, *Generic*
Intended indication(s): Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.4. Aripiprazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003899, *Generic*
Intended indication(s): Treatment of schizophrenia and treatment and prevention of manic episodes in bipolar I disorder

14.1.5. Asfotase alfa

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003794, *Orphan*
Intended indication(s): Treatment for long-term enzyme replacement therapy in patients with paediatric-onset hypophosphatasia

14.1.6. Atazanavir, cobicistat

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003904
Intended indication(s): Treatment of human immunodeficiency virus (HIV-1) infected adults aged 18 years and older in combination with other antiretroviral medicinal products

14.1.7. Eliglustat

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003724, *Orphan*
Intended indication(s): Treatment of Gaucher disease type 1

14.1.8. Empagliflozin, metformin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003770
Intended indication(s): Treatment of type II diabetes

14.1.9. Lamivudine, raltegravir

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003823
Intended indication(s): Treatment of human immunodeficiency virus (HIV-1)

14.1.10. Levofloxacin

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002789, *Orphan*
Intended indication(s): Treatment of chronic pulmonary infections

14.1.11. Nintedanib

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003821, *Orphan*
Intended indication(s): Treatment of idiopathic pulmonary fibrosis (IPF)

14.1.12. Ombitasvir, paritaprevir, ritonavir

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003839
Intended indication(s): Treatment of chronic hepatitis C

14.1.13. Ospemifene

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002780
Intended indication(s): Treatment of vulvar and vaginal atrophy (VVA)

14.1.14. Pegaspargase

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003789
Intended indication(s): Therapy in acute lymphoblastic leukaemia (ALL) in children, adolescents and adult patients

14.1.15. Pegfilgrastim

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003910, *informed consent*
Intended indication(s): Treatment of neutropenia

14.1.16. Rasagiline

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003957, *informed consent*
Intended indication(s): Treatment of Parkinson's disease

14.1.17. Safinamide

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002396
Intended indication(s): Treatment of Parkinson’s disease (PD)

14.1.18. Secukinumab

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003729
Intended indication(s): Treatment of plaque psoriasis

14.1.19. Sufentanil

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002784, *Hybrid*
Intended indication(s): Management of moderate to severe acute pain

14.1.20. Susoctocog alfa

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002792
Intended indication(s): Treatment of haemophilia A

14.1.21. Voriconazole

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/003737, *Generic*
Intended indication(s): Treatment of fungal infections

14.1.22. Vorapaxar

- Evaluation of an RMP in the context of an initial marketing authorisation application procedure

Administrative details:
Product number(s): EMEA/H/C/002814
Intended indication(s): Reduction of atherothrombotic events

Medicines already authorised

As per agreed criteria, the PRAC endorsed without further plenary discussion the conclusions of the Rapporteur on the assessment of these updated versions of the RMP for the below mentioned medicines.

RMP in the context of a variation[35] – PRAC-led procedure

14.1.23. Alglucosidase alfa – MYOZYME (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000636/II/0052
Procedure scope: Update to the RMP (version 7.2)
MAH(s): Genzyme Europe BV

14.1.24. Filgrastim – GRASTOFIL (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002150/II/0007

[35] In line with the revised variation regulation for submissions as of 4 August 2013

Procedure scope: Update of the RMP (version 5.3) to reflect class-specific safety updates made in the Grastofil product information in line with the Neupogen product information
MAH(s): Apotex Europe BV

14.1.25. Insulin human – INSUMAN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Jean-Michel Dogné (BE)

Administrative details:
Procedure number(s): EMEA/H/C/000201/II/0102
Procedure scope: Update of the RMP (version 2.0) for Insuman Implantable 400 IU/ml
MAH(s): Sanofi-aventis Deutschland GmbH

14.1.26. Micafungin – MYCAMINE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000734/II/0026
Procedure scope: Update of the RMP to amend the important identified risk of drug interaction, to include a second survey that will be conducted in Q1 2015 to further assess the effectiveness of risk minimization measures as requested by the PRAC in May 2014
MAH(s): Astellas Pharma Europe B.V.

14.1.27. Romiplostim – NPLATE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): EMEA/H/C/000942/II/0045
Procedure scope: Type II variation to remove the existing education programme (physician education booklet and dosing calculator) as a condition. The RMP (version 14) is updated accordingly
MAH(s): Amgen Europe B.V.

14.1.28. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000955/II/0043
Procedure scope: Update to the currently approved RMP (version 16.2) with information from the final clinical study report (CSR) of study NA25220
MAH(s): Roche Registration Ltd

14.1.29. Tenofovir disoproxil – VIREAD (CAP)
Emtricitabine, tenofovir disoproxil – EVIPLERA(CAP), **TRUVADA** (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000419/WS0598/0141/G, EMEA/H/C/002312/WS0598/0048/G, EMEA/H/C/000594/WS0598/0107/G
Procedure scope: Worksharing variation to: 1) update the RMP to remove study 174-0127 on renal safety; add references to studies previously submitted, add intermediate results for APR and MITOC studies and correct the classification from category 3 to 4 of the 7 studies (in the RMP for Eviplera and Truvada); 2) update the deadline for the final submission of study 104-0423 in the RMP
MAH(s): Gilead Sciences International Ltd

RMP in the context of a variation – CHMP-led procedure

14.1.30. Bedaquiline – SIRTURO (CAP)

- Evaluation of an RMP in the context of variation

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002614/II/0004/G
Procedure scope: Update of SmPC sections 4.4, 4.8 and 5.1 to reflect the final results of study TMC207-C208 stage 2 and study TMC207-C209. The MAH also took the opportunity to clarify the statement in SmPC section 4.5 related to the interaction of bedaquiline and lopinavir/ritonavir
MAH(s): Janssen-Cilag International N.V.

14.1.31. Bosentan – TRACLEER (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/000401/II/0066
Procedure scope: Extension of indication to include treatment of symptomatic pulmonary arterial hypertension in paediatric patients aged from 3 months to 18 years. The SmPC has been updated in order to include the data generated in studies conducted according to the agreed paediatric investigation plan for bosentan (EMEA-000425-PIP02-10-M04). As a consequence, SmPC sections 4.1, 4.2, 4.5, 4.8, 5.1, 5.2, 5.3 and 6.6 have been updated. The package leaflet has been updated accordingly. In addition, taking into account the new data in the paediatric population, .the RMP (version 5) is updated accordingly
MAH(s): Actelion Registration Ltd.

14.1.32. Colestilan – BINDREN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002377/II/0006/G
Procedure scope Group of variations to update SmPC section 4.5 to include the results of a completed drug-drug interaction study with colestilan and candesartan. In addition, update of section 5.1 in order to include the ATC code and pharmacotherapeutic classification. The RMP has been updated to include the results of the mentioned drug-drug interaction study. The package leaflet is updated accordingly
MAH(s): Mitsubishi Tanabe Pharma Europe Ltd

14.1.33. Dabigatran – PRADAXA (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Torbjorn Callreus (DK)

Administrative details:
Procedure number(s): EMEA/H/C/000829/II/0066
Procedure scope: Final clinical study report (CSR) for study 1160.86 (open label, non-comparative pharmacokinetic and pharmacodynamic study to evaluate the effect of Pradaxa on coagulation parameters including a calibrated thrombin time test in patients with moderate renal impairment undergoing primary unilateral elective total knee or hip replacement surgery). The RMP (version 28.6) is updated accordingly
MAH(s): Boehringer Ingelheim International GmbH

14.1.34. Darbapoetin alfa – ARANESP (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000332/II/0130
Procedure scope: Update of SmPC sections 4.2, 4.8, 5.1 and 5.2 to incorporate dosing recommendations for paediatric patients from 1 to < 11 years and to reflect the available data in the paediatric population, following the submission of the clinical study report of the paediatric study 20050256. The package leaflet and RMP are updated accordingly. Additionally, the MAH took the opportunity to implement the latest QRD template and to correct typographical errors in the product information
MAH(s): Amgen Europe B.V.

14.1.35. Dibotermin alfa – INDUCTOS (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000408/II/0071
Procedure scope: Extension of indication to broaden the use of Inductos in interbody lumbar spine fusion
MAH(s): Medtronic BioPharma B.V.

14.1.36. Febuxostat – ADENURIC (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:
Procedure number(s): EMEA/H/C/000777/II/0037
Procedure scope: Update of SmPC sections 4.1, 4.2, 4.4, 4.5, 4.8 and 5.1 for the 120 mg strength further to the introduction of a new indication for prevention and treatment of hyperuricaemia in adult patients undergoing chemotherapy for haematologic malignancies at intermediate to high risk of tumour lysis syndrome (TLS)
MAH(s): Menarini International Operations Luxembourg S.A.

14.1.37. Ibandronic acid – IBANDRONIC ACID ACCORD (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Product number(s): EMEA/H/C/002638/X/0006
Procedure scope: Line extension to add a new strength/potency and a new pharmaceutical form 3 mg solution for injection
Applicant: Accord Healthcare Ltd

14.1.38. Ivacaftor – KALYDECO (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:
Procedure number(s): EMEA/H/C/002494/II/0031
Procedure scope: Update of SmPC sections 4.8 and 5.1 to reflect the results of part 2 of study VX12-770-111 as a fulfilment of the post-authorisation measure (PAM) MEA 007
MAH(s): Vertex Pharmaceuticals (U.K.) Ltd.

14.1.39. Lipegfilgrastim – LONQUEX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002556/II/0004
Procedure scope: Update of SmPC sections 4.4 and 4.8 upon PRAC's request in order to include information regarding capillary leakage syndrome (CLS); a class effect of G-CSFs. The package leaflet is updated accordingly. The RMP (version 7.1) is also updated accordingly
MAH(s): Sicor Biotech UAB

14.1.40. Methylnaltrexone – RELISTOR (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Valerie Strassmann (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000870/II/0030
Procedure scope: Extension of indication for the treatment of opioid induced constipation in adult non cancer pain patients. Consequently, the MAH proposed the update of SmPC sections 4.1, 4.2, 4.4 and 5.1. The package leaflet is updated accordingly
MAH(s): TMC Pharma Services Ltd

14.1.41. Ocriplasmin – JETREA (CAP)

- Evaluation of an RMP in the context of a variation, line extension

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002381/X/0013
Procedure scope: Introduction of a ready-to-use (RTU) formulation with adjusted fill volume for Jetrea 0.375 mg/0.3 mL
MAH(s): ThromboGenics NV

14.1.42. Paliperidone – INVEGA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000746/II/0043
Procedure scope: Update of SmPC sections 4.1 in order to extend the indication to include depressive symptom domain of schizoaffective disorder. Additionally SmPC section 5.1 has been updated to reflect the data from study SCA-3004 on paliperidone palmitate effects in the maintenance of symptom control
MAH(s): Janssen-Cilag International N.V.

14.1.43. Ruxolitinib – JAKAVI (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002464/II/0017/G
Procedure scope: Grouped variations to update SmPC sections 4.5 and 5.2 based on the drug-drug interaction studies CINC424A2102, undertaken to evaluate the effects of ruxolitinib on the pharmacokinetics of a monophasic oral contraceptive, and CINC424A2103, undertaken to evaluate the intestinal CYP3A4 inhibitory effect of ruxolitinib on the pharmacokinetics of orally administered midazolam. The RMP (version 3.1) is updated accordingly
MAH(s): Novartis Europharm Ltd

14.1.44. Shingles (herpes zoster) vaccine (live) – ZOSTAVAX (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000674/II/0077
Procedure scope: Update of SmPC sections 4.3, 4.4, 4.8 and 5.1 to reflect the results of a double blind placebo controlled study to investigate the immunogenicity, and safety of Zostavax in subjects with HIV infection to address a post-authorisation measure in the RMP. The MAH took the opportunity to perform other updates of the RMP: to classify herpes zoster/herpes zoster like rash and varicella/varicella-like rash as an important identified risk and to reflect in the RMP the results of 2 other clinical studies with implications for safety concerns (protocol 029 a booster dose study and protocol 016)
MAH(s): Sanofi Pasteur MSD SNC

14.1.45. Ulipristal – ELLAONE (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Menno van der Elst (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001027/II/0021
Procedure scope: Change in the classification for supply from 'medicinal product subject to medical prescription' to 'medicinal product not subject to medical prescription' in the EU. Update of the product information in line with a non-prescription setting. Updates of SmPC sections 4.2, 4.4 and 5.1 based on repeated use study (protocol 091015-001) and on interim data from the STEella study in post-menarcheal girls and adult women (protocol 2914-010)
MAH(s): Laboratoire HRA Pharma, SA

14.1.46. Ulipristal – ESMYA (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002041/II/0028
Procedure scope: Update of SmPC section 4.1 with subsequent updates to sections 4.2, 4.4, 4.8 and 5.1 in order to extend the current indication to long term (repeated intermittent) treatment of moderate to severe symptoms of uterine fibroids in adult women of reproductive age
MAH(s): Gedeon Richter Plc.

14.1.47. Tobramycin – TOBI PODHALER (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002155/II/0027/G
Procedure scope: Update of SmPC sections 4.2, 4.4 and 4.8 of in order to reflect data from study CTBM100C2401 (in fulfilment of MEA 10)
MAH(s): Novartis Europharm Ltd

14.1.48. Trastuzumab – HERCEPTIN (CAP)

- Evaluation of an RMP in the context of a variation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000278/II/0084/G
Procedure scope: Update of SmPC sections 4.2 and 4.8 with information on switching between intravenous (IV) and subcutaneous (SC) formulations further to safety data from study MO22982. The package leaflet is updated accordingly. Update of SmPC section 4.2 with a statement regarding switching between Herceptin and biosimilars
MAH(s): Roche Registration Ltd

14.1.49. Travoprost – TRAVATAN (CAP)

- Evaluation of an RMP in the context of a variation, extension of indication

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): EMEA/H/C/000390/II/0046
Procedure scope: Extension of the therapeutic indication for decrease of elevated intraocular pressure in paediatric patients with ocular hypertension or paediatric glaucoma
MAH(s): Alcon Laboratories (UK) Ltd

RMP evaluated in the context of a renewal of the marketing authorisation, conditional renewal or annual reassessment

14.1.50. Eltrombopag – REVOLADE (CAP)

- Evaluation of an RMP on the context of a five year-renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): EMEA/H/C/001110/R/0018
MAH(s): GlaxoSmithKline Trading Services

14.1.51. Zoledronic acid – ACLASTA (CAP)

- Evaluation of an RMP in the context of a five year-renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000595/R/0051 (with RMP)
MAH(s): Novartis Europharm Ltd

See also: Denosumab - PROLIA 8.1.1.

15. ANNEX I Assessment of Periodic Safety Update Reports (PSURs)

Based on the assessment of the following PSURs, the PRAC concluded that the benefit-risk balance of the below mentioned medicines remains favourable in the approved indication(s) and adopted a

recommendation to maintain the current terms of the marketing authorisation(s) together with the assessment report. As per agreed criteria, the procedures listed below were finalised at the PRAC level without further plenary discussion.

The next PSURs should be submitted in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal, unless changes apply as stated under relevant PSUR procedure(s).

Evaluation of PSUR procedures

15.1.1. Abiraterone – ZYTIGA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Dolores Montero Corominas (ES)

Administrative details:
Procedure number(s): EMEA/H/C/002321/PSUV/0024
MAH(s): Janssen-Cilag International N.V.

15.1.2. Alipogene tiparvovec – GLYBERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002145/PSUV/0036
MAH(s): uniQure biopharma B.V.

15.1.3. Bortezomib – VELCADE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Carmela Macchiarulo (IT)

Administrative details:
Procedure number(s): EMEA/H/C/000539/PSUV/0073
MAH(s): Janssen-Cilag International N.V.

15.1.4. Catumaxomab – REMOVAB (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000972/PSUV/0021
MAH(s): Neovii Biotech GmbH

15.1.5. Ceftaroline fosamil – ZINFORO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002252/PSUV/0019
MAH(s): AstraZeneca AB

15.1.6. Colestilan – BINDREN (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002377/PSUV/0005 (with RMP version 4.0)
MAH(s): Mitsubishi Tanabe Pharma Europe Ltd

15.1.7. Dapagliflozin – FORXIGA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002322/PSUV/0014
MAH(s): Bristol-Myers Squibb/AstraZeneca EEIG

15.1.8. Defibrotide – DEFITELIO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002393/PSUV/0003
MAH(s): Gentium S.p.A.

15.1.9. Ertapenem – INVANZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000389/PSUV/0051
MAH(s): Merck Sharp & Dohme Limited

15.1.10. Febuxostat – ADENURIC (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Jan Neuhauser (AT)

Administrative details:
Procedure number(s): EMEA/H/C/000777/PSUV/0035
MAH(s): Menarini International Operations Luxembourg S.A.

15.1.11. Fesoterodine – TOVIAZ (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:
Procedure number(s): EMEA/H/C/000723/PSUV/0042
MAH(s): Pfizer Limited

15.1.12. Histamine dihydrochloride – CEPLENE (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000796/PSUV/0021 (with RMP version 7.0)
MAH(s): Meda AB

15.1.13. Insulin glulisine – APIDRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000557/PSUV/0060
MAH(s): Sanofi-aventis Deutschland GmbH

15.1.14. Japanese encephalitis vaccine (inactivated, adsorbed) – IXIARO (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000963/PSUV/0062
MAH(s): Valneva Austria GmbH

15.1.15. Mannitol – BRONCHITOL (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001252/PSUV/0014
MAH(s): Pharmaxis Pharmaceuticals Limited

15.1.16. Meningococcal group a, c, w135 and y conjugate vaccine – NIMENRIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002226/PSUV/0027
MAH(s): GlaxoSmithKline Biologicals S.A.

15.1.17. Ocriplasmin – JETREA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002381/PSUV/0014
MAH(s): ThromboGenics NV

15.1.18. Ofatumumab – ARZERRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Doris Stenver (DK)

Administrative details:
Procedure number(s): EMEA/H/C/001131/PSUV/0030
MAH(s): Glaxo Group Ltd

15.1.19. Olanzapine – ZYPADHERA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Terhi Lehtinen (FI)

Administrative details:
Procedure number(s): EMEA/H/C/000890/PSUV/0024 (with RMP version 11.0)
MAH(s): Eli Lilly Nederland B.V.

15.1.20. Panitumumab – VECTIBIX (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000741/PSUV/0062
MAH(s): Amgen Europe B.V.

15.1.21. Parecoxib – DYNASTAT (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000381/PSUV/0062 (with RMP version 4.0)
MAH(s): Pfizer Limited

15.1.22. Pasireotide – SIGNIFOR (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002052/PSUV/0015
MAH(s): Novartis Europharm Ltd

15.1.23. Tadalafil – ADCIRCA (CAP), **CIALIS** (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Miguel-Angel Macia (ES)

Administrative details:
Procedure number(s): EMEA/H/C/001021/PSUV/0019, EMEA/H/C/000436/PSUV/0076
MAH(s): Eli Lilly Nederland B.V.

15.1.24. Tocilizumab – ROACTEMRA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000955/PSUV/0041
MAH(s): Roche Registration Ltd

15.1.25. Vandetanib – CAPRELSA (CAP)

- Evaluation of a PSUR procedure

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002315/PSUV/0010
MAH(s): AstraZeneca AB

15.2. Follow-up to PSUR procedures[36]

15.2.1. **Plerixafor – MOZOBIL** (CAP)

- Evaluation of a follow-up to a PSUR procedure

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/001030/LEG 024
Procedure scope: Evaluation of the MAH's response to request for supplementary information to PSU 017 (PSUR#7) previously adopted at PRAC
MAH(s): Genzyme Europe BV

16. ANNEX I Post-authorisation Safety Studies (PASS)

Since all comments received on the assessment of these studies were addressed before the plenary meeting, the PRAC endorsed the conclusion of the Rapporteurs on the assessment of the relevant protocol or study report for the medicines listed below without further plenary discussion.

16.1.1. **Albiglutide – EPERZAN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002735/MEA 002
Procedure scope: Evaluation of a PASS protocol for an observational database study (non-interventional cohort) (protocol PRJ2335) to assess the risk of acute pancreatitis in subjects exposed to albiglutide, other GLP-1 agonists or DPP-4 inhibitors compared to other antidiabetic agents
MAH(s): GlaxoSmithKline Trading Services

16.1.2. **Albiglutide – EPERZAN** (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002735/MEA 003
Procedure scope: Evaluation of a PASS protocol for a phase IV observational database study (non-interventional cohort,) (Protocol PRJ2331) to assess the risk of thyroid and pancreatic cancers, and malignancy when used in combination with insulins in observational databases of sufficient size that provides long term longitudinal follow up of patients
MAH(s): GlaxoSmithKline Trading Services

16.1.3. **Albiglutide – EPERZAN** (CAP)

- Evaluation of a PASS protocol

[36] Follow-up as per the conclusions of the previous PSUR procedure, assessed outside of the next PSUR procedure

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002735/MEA 004
Procedure scope: Evaluation of a PASS protocol for a phase IV observational drug utilisation and foetal outcome study (non-interventional cohort) (protocol PRJ2376) to assess the proportion and characteristic of type2 diabetic women of childbearing potential who are prescribed albiglutide
MAH(s): GlaxoSmithKline Trading Services

16.1.4. Albiglutide – EPERZAN (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002735/MEA 005
Procedure scope: Evaluation of a PASS protocol for a phase IV observational drug utilisation and foetal outcome study (non-interventional cohort) (protocol PRJ2379) to assess the proportion and characteristics of type 2 diabetic women who are exposed to albiglutide during pregnancy
MAH(s): GlaxoSmithKline Trading Services

16.1.5. Catridecacog – NOVOTHIRTEEN (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Arnaud Batz (FR)

Administrative details:
Procedure number(s): EMEA/H/C/002284/MEA 003.3
Procedure scope: Evaluation of a revised PASS protocol for a prospective multi-centre observational study on treatment of congenital FXIII deficiency (NN1841-3868)
MAH(s): Novo Nordisk A/S

16.1.6. Influenza vaccine (surface antigen, inactivated, prepared in cell cultures) – OPTAFLU (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000758/MEA 041.3
Procedure scope: Evaluation of the MAH's response to MEA-041.2 (study V58_30OB protocol replacing study V58P14) following the request for supplementary information adopted at PRAC in January 2014
MAH(s): Novartis Vaccines and Diagnostics GmbH

16.1.7. Voriconazole – VFEND (CAP)

- Evaluation of a PASS protocol

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/000387/MEA 087.1
Procedure scope: Evaluation of a revised PASS protocol (study A1501020): effectiveness of risk minimisation measures aiming at reducing the risks of phototoxicity, squamous cell carcinoma (SCC) of the skin and hepatic toxicity in patients receiving voriconazole in EU
MAH(s): Pfizer Limited

16.1.8. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)
pioglitazone, glimepiride – **TANDEMACT** (CAP)
pioglitazone, metformin – **COMPETACT** (CAP), **GLUBRAVA** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/WS0646/0065, EMEA/H/C/000286/WS0646/0063, EMEA/H/C/000680/WS0646/0040, EMEA/H/C/000655/WS0646/0050, EMEA/H/C/000893/WS0646/0036 (with RMP)
Procedure scope: Evaluation of the results of study AD-4833-411: drug utilisation study on the use of pioglitazone in clinical practice in the UK after the labelling change dated July 2011. The RMP is updated accordingly to reflect the finalisation of the study
MAH(s): Takeda Pharma A/S

16.1.9. Pioglitazone – ACTOS (CAP), **GLUSTIN** (CAP)
pioglitazone, glimepiride – **TANDEMACT** (CAP)
pioglitazone, metformin – **COMPETACT** (CAP), **GLUBRAVA** (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Almath Spooner (IE)

Administrative details:
Procedure number(s): EMEA/H/C/000285/WS0647, EMEA/H/C/000286/WS0647, EMEA/H/C/000680/WS0647, EMEA/H/C/000655/WS0647, EMEA/H/C/000893/WS0647 (with RMP)
Procedure scope: Evaluation of study 01-03-TL-OPI-524: cohort study of pioglitazone and bladder cancer in patients with diabetes, and updated RMP in order to reflect the finalisation of the study
MAH(s): Takeda Pharma A/S

16.1.10. Regorafenib – STIVARGA (CAP)

- Evaluation of PASS results

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002573/II/0005 (with RMP)
Procedure scope: Evaluation of the final results of study 14814 (cardiovascular safety study, category 3): evaluation of the effect of regorafenib on cardiovascular safety parameters, specifically QT/QTc intervals and left ventricular ejection fraction (LVEF)
MAH(s): Bayer Pharma AG

16.1.11. Adalimumab – HUMIRA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000481/MEA 075.3
Procedure scope: Second annual progress report for a long-term non-interventional registry to assess safety and effectiveness of adalimumab in patients with moderately to severely active ulcerative colitis (UC)
MAH(s): AbbVie Ltd.

16.1.12. Certolizumab pegol – CIMZIA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/00103/MEA 005.1
Procedure scope: Evaluation of interim reports from ARTIS (RA0021), RABBIT (RA0020), US National Databank for Rheumatic Diseases (RA0005) and BSRBR (RA0022)
MAH(s): UCB Pharma SA

16.1.13. Cobicistat – TYBOST (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/2572/MEA 013.1
Procedure scope: Interim report on the antiretroviral pregnancy registry (APR)
MAH(s): Gilead Sciences International Ltd

16.1.14. Elvitegravir – VITEKTA (CAP)
elvitegravir, cobicistat, emtricitabine, tenofovir - **STRIBILD** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/002577/MEA 009.1, EMEA/H/C/002574/MEA 013.1
Procedure scope: Interim report on the antiretroviral pregnancy registry (APR)
MAH(s): Gilead Sciences International Ltd

16.1.15. Emtricitabine – EMTRIVA (CAP)
emtricitabine, tenofovir – TRUVADA (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Rafe Suvarna (UK)

Administrative details:
Procedure number(s): EMEA/H/C/000533/MEA 047.1, EMEA/H/C/000594/MEA 040.1

Procedure scope: Interim report on the antiretroviral pregnancy registry (APR)
MAH(s): Gilead Sciences International Ltd

16.1.16. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000992/MEA 005.3
Procedure scope: Fourth annual report on a German registry study RABBIT to study the long term safety of biologics
MAH(s): Janssen Biologics B.V.

16.1.17. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000992/MEA 006.2
Procedure scope: Third annual report of a registry study of the Swedish database initiative for exposure to golimumab: review and analysis of adverse events from the Swedish National registry system (CNTOART4003)
MAH(s): Janssen Biologics B.V.

16.1.18. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000992/MEA 007
Procedure scope: First annual report on a pregnancy research initiative to study the exposure to golimumab during pregnancy in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: review and analysis of birth outcomes from the Swedish, Danish, and Finnish medical birth registers (CNTO148ART4001)
MAH(s): Janssen Biologics B.V.

16.1.19. Golimumab – SIMPONI (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Ulla Wändel Liminga (SE)

Administrative details:
Procedure number(s): EMEA/H/C/000992/MEA 008.1
Procedure scope: First annual report on i3 drug safety epidemiology study (CNTO148ART4002), prospective observational study using a large US health insurance claims database to estimate the long term safety profile in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis initiating golimumab and other types of biological and non-biological treatments after the launch of golimumab

MAH(s): Janssen Biologics B.V.

16.1.20. **Human fibrinogen, human thrombin – EVICEL** (CAP)

- Evaluation of interim PASS results

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/000898/MEA 008.3
Procedure scope: Progress report on a post-authorisation safety surveillance (PASS): observational, non-interventional study in vascular surgery
MAH(s): Omrix Biopharmaceuticals N. V.

17. ANNEX I Renewals of the Marketing Authorisation, Conditional Renewals and Annual Reassessments

Based on the review of the available pharmacovigilance data for the medicines listed below and the CHMP Rapporteur's assessment report, the PRAC considered that either the renewal of the marketing authorisation procedure could be concluded - and supported the renewal of their marketing authorisations for an unlimited or additional period, as applicable - or no amendments to the specific obligations of the marketing authorisation under exceptional circumstances for the medicines listed below were recommended. As per agreed criteria, the procedures were finalised at the PRAC level without further plenary discussion.

17.1.1. **Amifampridine – FIRDAPSE** (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Julie Williams (UK)

Administrative details:
Procedure number(s): EMEA/H/C/001032/S/0027 (without RMP)
MAH(s): BioMarin Europe Ltd

17.1.2. **Bedaquiline – SIRTURO** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Qun-Ying Yue (SE)

Administrative details:
Procedure number(s): EMEA/H/C/002614/R/0003 (without RMP)
MAH(s): Janssen-Cilag International N.V.

17.1.3. **Bosutinib – BOSULIF** (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Martin Huber (DE)

Administrative details:
Procedure number(s): EMEA/H/C/002373/R/0010 (without RMP)
MAH(s): Pfizer Limited

17.1.4. Cabozantinib – COMETRIQ (CAP)

- PRAC consultation on a conditional renewal of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Sabine Straus (NL)

Administrative details:
Procedure number(s): EMEA/H/C/002640/R/0009 (without RMP)
MAH(s): TMC Pharma Services Ltd

17.1.5. Canakinumab – ILARIS (CAP)

- PRAC consultation on an annual reassessment of the marketing authorisation

Regulatory details:
PRAC Rapporteur: Brigitte Keller-Stanislawski (DE)

Administrative details:
Procedure number(s): EMEA/H/C/001109/S/0035 (without RMP)
MAH(s): Novartis Europharm Ltd

ANNEX II – List of participants:

Including any restrictions with respect to involvement of members / alternates / experts following evaluation of declared interests for the 3 - 6 November 2014 meeting.

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies Product/ substance***
June Munro Raine	Chair	Full involvement	
Harald Herkner	Austria	Full involvement	
Jean-Michel Dogné	Belgium	Cannot act as Rapporteur or Peer Reviewer for:	octocog alfa, radium-223 dichloride, sorafenib, telmisartan, hydrochorothiazide, regorafenib
Veerle Verlinden	Belgium	Full involvement	
Maria Popova-Kiradjieva	Bulgaria	Full involvement	
Viola Macolić Šarinić	Croatia	Full involvement	
Jana Mladá	Czech Republic	Full involvement	
Doris Stenver	Denmark	Full involvement	
Torbjörn Callreus	Denmark	Full involvement	
Maia Uusküla	Estonia	Full involvement	
Terhi Lehtinen	Finland	Full involvement	
Kirsti Villikka	Finland	Full involvement	
Arnaud Batz	France	Cannot act as Rapporteur or Peer Reviewer for:	infliximab, golimumab, paliperidone, bedaquiline, abiraterone, bortezomib
Patrick Maison	France	Full involvement	
Martin Huber	Germany	Full involvement	
Valerie Strassmann	Germany	Full involvement	
Agni Kapou	Greece	Full involvement	
Julia Pallos	Hungary	Cannot act as Rapporteur or Peer Reviewer for:	aripiprazole
Guðrún Kristín Steingrímsdóttir	Iceland	Full involvement	
Almath Spooner	Ireland	Full involvement	
Ruchika Sharma	Ireland	Full involvement	
Carmela Macchiarulo	Italy	Full involvement	
Andis Lacis	Latvia	Cannot act as Rapporteur or	clarithromycin

PRAC member PRAC alternate	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
		Peer Reviewer for:	
Jolanta Gulbinovic	Lithuania	Full involvement	
Jacqueline Genoux-Hames	Luxembourg	Full involvement	
Amy Tanti	Malta	Full involvement	
Sabine Straus	Netherlands	Full involvement	
Menno van der Elst	Netherlands	Full involvement	
Ingebjørg Buajordet	Norway	Full involvement	
Karen Pernille Harg	Norway	Full involvement	
Magdalena Budny	Poland	Full involvement	
Margarida Guimarães	Portugal	Full involvement	
Roxana Stroe	Romania	Full involvement	
Tatiana Magálová	Slovakia	Full involvement	
Milena Radoha-Bergoč	Slovenia	Full involvement	
Dolores Montero Corominas	Spain	Full involvement	
Miguel-Angel Maciá	Spain	Full involvement	
Qun-Ying Yue	Sweden	Full involvement	
Ulla Wändel Liminga	Sweden	Full involvement	
Julie Williams	United Kingdom	Full involvement	
Rafe Suvarna	United Kingdom	Full involvement	

Independent scientific experts nominated by the European Commission	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting:***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Jane Ahlqvist Rastad	Not applicable	Full involvement	
Marie Louise De Bruin		Full involvement	
Stephen Evans		Cannot act as Rapporteur or Peer reviewer for:	plasmodium falciparum circumsporozoite protein fused with hepatitis B surface antigen (rts), and combined with hepatitis B surface antigen (s) in the form of non-infectious virus-like particles (vlps) produced in yeast cells (saccharomyces cerevisiae) by recombinant DNA technology; eltrombopag; meningococcal group a, c, w135 and y conjugate vaccine; ofatumumab; umeclidinium bromide, vilanterol; albiglutide
Birgitte Keller-Stanislawski		Full involvement	
Herve Le Louet		Full involvement	

Health care professionals and patients members	***Country***	***Outcome restriction following evaluation of e-DoI for the meeting:***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/substance***
Filip Babylon		Full involvement	
Marco Greco		Full involvement	
Kristen Myhr		Full involvement	
Albert van der Zeijden		Cannot act as Rapporteur or Peer Reviewer in relation to any medicinal product from the relevant companies for which his institution receives grants as listed in the published Declaration of Interest (16-05-2014) http://www.ema.europa.eu/docs/en_GB/document_library/contacts/avanderzeijden_DI.pdf	

Additional European experts participating at the meeting for specific Agenda items	***Country***	***Topics on the current Committee Agenda for which restriction applies*** ***Product/ substance***
Christelle Bizimungu	Belgium	
Corinne Fechant	France	
Mélanie Leplay	France	
Jens Rotthauwe	Germany	
Franz Kleber	Germany	
Vera Luetgendorf	Germany	
Sayed Tabatabaei	Netherlands	
Frank Holtkamp	Netherlands	
Peter Mol	Netherlands	
Jana Nováková	Slovakia	
Ivana Pankuchova	Slovakia	
Charlotte Backman	Sweden	
Angelika Siapkara	United Kingdom	
Juliana Min	United Kingdom	
Alie Banner Simpson	United Kingdom	
Patrick Batty	United Kingdom	
Max Lagnado	United Kingdom	
Rob Hemmings	United Kingdom	

ANNEX III – List of abbreviations

For a List of the acronyms and abbreviations used in the PRAC (Pharmacovigilance Risk Assessment Committee) Minutes used in the PRAC minutes, see:

www.ema.europa.eu

Home>About Us>Committees>PRAC Agendas, minutes and highlights